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From the Pediatric Clinic of the University of Athens.
Director: Professor C. V. CHOREMIS

Does Prophylactic Vaccination Favour the Development of Poliomyelitis?

by C. CHOREMIS and PH. NICOLAIDES

During the months of October, November and December, 1950, an epidemic of diphtheria appeared in Greece. Prophylactic inoculation was started on a big scale with triple vaccine (diphtheria, whooping-cough and tetanus).

Poliomyelitis had been endemic in Greece until 1949. An epidemic occurred during the months of October, November, December, 1949, and January, February, 1950. The epidemic subsided during the winter and summer of 1950. During the autumn of 1950 an increase in the number of cases of pyliomyelitis occurred. It is interesting that while the few cases occurring during the endemic period March—November, 1950, came from all parts of Greece, almost all the cases during the autumn of 1950 came from Athens or its suburbs which was the only area of Greece, where prophylactic antidiphtheria immunisation was systematically done.

Table I shows the monthly cases of poliomyelitis and diphtheria admitted to the Children's Hospital during the years 1949 an 1950. From November 1950 to February 1951 76 cases of poliomyelitis were treated. Seventeen of these cases were recently vaccinated with the combined vaccine.

Case Histories

Case 1. — 18 months old. Vaccination November 30th 1950. Eight hours following the first dose developed a temperature of 39°—40°, which continued for 6 days. Paralysis of the right leg followed fall in temperature. Vaccination area: left thigh. C.S.F.: Alb. 0.40 ‰, cells 26.

Case 2. — 20 months old. Vaccination: 1st dose, right thigh on 13/11 1950. 2nd dose, left thigh 13/12 1950. 24 hours following the second dose temperature rose to 37°—38° with marked sweating. Temperature fell to normal three days later and paralysis of the right leg developed. C.S.F.: Alb. 0.20 ‰, cells 33.

Case 3. — 8 months old. Vaccinated in three doses on 18/11, 2/12 and 22/12 1950. Site of vaccination the right thigh. Three days following the last injection, temperature rose to 38°—39°5 and simultaneously paralysis of the left arm developed. C.S.F.: Alb. 0.40 ‰, cells 18.

TABLE 1

The monthly number of cases of poliomyelitis and diphtheria admitted to the Children's Hospital during the years 1949 and 1950.

			Poliomyelitis cases	Diphtheria cases
1949	July		0	16
	August		1	12
	September		4	16
	October	Poliomyelitis epidemic	17	31
	November		101	38
	December		63	40
1950	January		14	53
	February		30	45
	July		11	22
	August		8	28
	September		7	31
	October	Diphtheria epidemic	8	127
	November		9	216[1]
	December		30	123[1]
1951	January		18	43
	February		19	18

[1] Vaccination during November and half of December.

Case 4. — 3 years of age. Vaccinated with combined vaccine 18/11 1950. Three days later, strabismus developed with limitation of head movement and paresis of the legs. Vaccination area, right thigh. C.S.F.: Alb. 0.15 ‰, cells 8.

Case 5. — 7 years of age. First dose of vaccine given 20/12 1950 on the right thigh. Second dose given 4/1 1951 on the left thigh. Three days later he developed paresis of both arms and right leg with rigidity of the neck.

Case 6. — 9 months old. Combined vaccine administered in two doses. The first one on 17/11 1950 on the right thigh and the second on 12/12 1950 on the left thigh. Three days later there developed a high temperature, 39—40°, with weakness of the voice, paralysis of the muscles of the neck, the respiratory muscles and tetraplegy. C.S.F.: Alb. 0.30 ‰, cells 8.

Case 7. — 2 1/2 years of age. First injection of combined vaccine given 17/11 1950 on the right arm. Five days after vaccination development of high temperature, pains in the upper and lower extremities, vomiting, retention of urine, paralysis of the neck and respiratory muscles, and tetraplegy. C.S.F.: Alb. 0.45 ‰, cells 48.

Case 8. — 18 months old. Combined vaccine given in three doses: 1) 10/11 1950 on the left thigh. 2) 20/12 1950 on the left thigh and 3) 10/1 1951 on the right thigh. Nine days following the last dose development of temperature, rigidity of the neck and paralysis of the right leg. C.S.F.: Alb. 0.40 ‰, cells 160.

Case 9. — 20 months old. First dose of vaccine given 17/11 1950 on the right thigh. Nine days following vaccination development of a temperature of 38°—38°5, which lasted 7 days, constipation, weakening of the voice, paralysis of the abdominal muscles and of the right leg. C.S.F.: Alb. 0.10 ‰, cells 132.

Case 10. — 10 months old. Combined vaccine given in two doses: 1) 21/11 1950 on the left thigh. 2) 23/12 1950 in the same area. Fever appeared 10 days following the second injection which lasted 3 days accompanied by paralysis of the left leg. C.S.F.: Alb. 0.25 ‰, cells 24.

Case 11. — 4 years old. Vaccine given in three doses, all on the left thigh: 1) 25/11 1950. 2) 10/12 1950. 3) 24/12 1950. Fever 39°—40° appeared 10 days following the third dose, with difficulty in passing urine, constipation, perspiration and rigidity of the neck and paralysis of both legs.

Case 12. — 18 months old. First dose given 23/11 1950 on the left arm. A temperature of 39°, paralysis of the upper limbs, the neck and intercostal muscles developed 10 days after vaccination. C.S.F.: Alb. 0.35 ‰, cells 45.

Case 13. — 18 months old. First dose of combined vaccine given 20/11 1950. A temperature of 39°—40° with gastrointestinal symptoms appeared 10 days following vaccination. The dropping of temperature was followed by paralysis of the right arm. C.S.F.: Alb. 0.35 ‰, cells 45.

Case 14. — 2 1/2 years old. Vaccinated twice: 21/11 1950 on the left thigh and 5/12 1950 on the right thigh. A temperature of 38°, which lasted 4 days, constipation, rigidity of the neck and paralysis of the left arm appeared 11 days following vaccination. C.S.F.: Alb. 0.40 ‰, cells 10.

Case 15. — 2 1/2 years old. Vaccine given in three doses. 5/12, 20/12 1950 and 5/1 1951: all given on the right arm. Fever lasting one day and paralysis of the right arm developed 29 days following the 3rd injection. C.S.F.: Alb. 0.20 ‰, cells 10.

Case 16. — 14 months old. Combined vaccine given in three doses. 20/11 on the right thigh, 10/12 1950 on the left thigh and 2/1 1951 on the right thigh. High fever appeared 40 days following the last dose; 4 days later tetraplegy, paralysis of the neck muscles and weakness of the voice. C.S.F.: Alb. 0.50 ‰, cells 8.

Case 17. — 6 years old. First dose given 1/12 1950 on the left thigh. 45 days following vaccination development of temperature with meningeal signs and paralysis of the right leg. C.S.F.: Alb. 0.30 ‰, cells 200.

Discussion

Various problems arise and are discussed under various headings.

1) Do these cases prove the harmful effect of vaccination on the development of poliomyelitis. There was an undoubted sudden increase in the number of cases during November and December (Table 2) but owing to their small number it is not possible to analyse them statistically. The short time between vaccination and the appearance of the disease, less than 15 days in all but two cases (Table 2) suggests that immunisation plays some part in the

TABLE 2

R.A. = right arm. L.A. = left arm. R.L = right leg. L.L. = left leg.

Case	Age	Time between injection & paralysis	Last limb injected	Paralysis on limb injected	Paralysis on limb not injected				Other paralysis
					R.A.	L.A.	R.L.	L.L.	
1	18 m.	8 hrs.	L.L.	0	0	0	+	0	0
2	20 m.	31 hrs.	R.L.	+	0	0	−	0	0
3	8 m.	3 days	R.L.	0	0	+	0	0	0
4	3 yrs.	3 »	R.L.	+	0	0	−	+	+
5	7 yrs.	3 »	L.L.	+	0	+	0	−	0
6	9 m.	3 »	L.L.	+	+	+	+	−	+
7	30 m.	5 »	R.A.	+	−	+	+	+	+
8	18 m.	9 »	R.L.	+	0	0	−	0	0
9	20 m.	9 »	R.L.	+	0	0	−	0	+
10	11 m.	10 »	L.L.	+	0	0	0	−	0
11	4 yrs.	10 »	L.L.	+	0	0	+	−	0
12	18 m.	10 »	L.A.	+	+	−	0	0	+
13	18 m.	12 »			0	0	0	+	0
14	30 m.	18 »	R.L.	0	0	+	0	0	0
15	30 m.	29 »	R.A.	+	−	0	0	0	0
16	14 m.	40 »	R.L.	+	+	+	−	+	+
17	6 yrs.	45 »	L.L.	0	0	0	+	0	0

development of the disease and therefore our observations agree with the reports of the other authors.

The localization of the paralysis is a good argument in favour of some relationship between the prophylactic vaccination and poliomyelitis.

From the analysis of our cases, following McClockey's method in relation to the localization of the disease, it is shown that while on the limbs vaccinated the relation between those affected and those non-affected is 12 : 4 or 3 : 1; on those not vaccinated in reverse is the case 17 : 31 or 1 : 2. Comparing only the lower limbs which is the common site of inoculation we observe that out of 13, 9 were attacked, whilst out of 19 non-vaccinated 8 were attacked.

The difference is more obvious as far as the upper limbs are concerned, where all of 3 vaccinated limbs were attacked and of 20 non-vaccinated only 9 were attacked. In 4 cases paralysis affected only the limb injected. On the contrary, on limbs non-vaccinated 4 single paralysis were observed; whilst the proportion should be 1 : 3, it was 1 : 1. On 7 cases paralysis appeared following the 1st injection, on 5 after the 2nd and on 5 after the 3rd (Tables 3 and 4).

2) The pathogenesis of paralysis following vaccination is more interesting. No definite conclusion can be reached. Many opinions and theories have been

TABLE 3

The period of time betwen the last injection and the appearance of the symptoms.

Days	1—15	16—30	31—45
No. of Cases . .	13	2	2

TABLE 4

The relation between the area vaccinated and the affected one.

Limbs	Vaccinated		Non-vaccinated	
	Affected	Non-affected	Affected	Non-affected
R.A. . . .	2	0	3	11
R.L. . . .	5	2	5	4
L.A. . . .	1	0	6	9
L.L. . . .	4	2	3	7
Total	12	4	17	31

put forward. HORSTMANN and PAUL believe that the local trauma of the injection, as well as any other wound or fatigue may cause alterations in the corresponding area of the spinal cord favouring the activation of the virus already existing in central nervous system.

RUSSEL expresses the same opinion, attributing the influence of the vaccine on the modification of the anterior horns of the spinal cord and especially of the nerve cells supplying the damaged area with the result that these become more susceptible to the virus.

It is fairly certain that any wound, independent of cause, favours the development of poliomyelitis. The role of tonsillectomy is considered proven (HORSTMANN). SIEGEL, GREENBERG and MAGEL have shown, after studying 53,007 tonsillectomies carried out in various hospitals in New York in 1949, that tonsillectomy plays a part in the development of poliomyelitis.

HARRINGTON has shown following the study of 100 cases of poliomyelitis that a preceeding wound has had an immediate relation to the area of the paralysis.

The type of the vaccine does not seem to be of particular importance. A much greater consideration is given on ways of vaccination; that is to say intramuscularly or hypodermically (MCCLOSKEY, MCLOED). The latter, during the poliomyelitis epidemic in Belfast, Northern Ireland, April-September

1950, on 6,250 antidiphtheria inoculations done with P.T.A.P. (purified toxoid aluminum precipitated) found no relation between the way of vaccination and disease. This vaccine is injected hypodermically.

BOUSFIELD is of the same opinion. He suggests the abandonment of the intramuscular injection of the antidiphtheria toxoid and prefers the hypodermic method with P.T.A.P.

We feel that the belief that trauma only plays a part is not the whole story. We believe that, besides the local injury, general resistance is lowered, especially with the combined vaccines. A reaction with a rise in temperature and severe clinical signs is not rare during mass inoculation.

Some workers in the past believed in a negative phase or anergy caused by the vaccine and examples of the development of the disease in connection with vaccines such as antityphoid or antidiphtheria, are to be found. It could then be possible to accept the activation of the virus already existing in the organism i.e., a latent infection become obvious, due to the known fact that the infection with the virus is widespread during epidemics. The neurotropism of the diphtheria and tetanus toxoids and that of the whooping-cough vaccine favours the specific or selective weakening of the organism toward the poliomyelitis virus, especially when these vaccines are given together in young individuals.

We have repeatedly observed, following the injection of combined vaccines, severe reactions with a high temperature lasting many days and also re-activation of an adenitis, and rarely reactions from the kidneys.

Summary

Seventy six cases of poliomyelitis have been admitted in St. Sophie Children's Hospital during the autumn of 1950. In seventeen of them there was a history of previous vaccination with mixed vaccine (pertussis-tetanus-diphtheria). The interval between vaccination and the appearance of paralysis was 2—14 days. In 75 % of the cases the paralysis occurred in the vaccinated limb.

Relation entre Vaccination et Poliomyélite. La vaccination prophylactique favorise-t-elle le développement de la poliomyélite?

Soixante-dix cas de poliomyélite ont été admis à l'Hôpital d'enfants de Ste. Sophie dans le courant de l'année 1950. Chez 17 d'entre eux, on a retrouvé une histoire de vaccination antérieure avec vaccin mixte (coqueluche-tétanos-diphtérie). L'intervalle entre vaccination et début des paralysies était de 2 à 14 jours. Dans 75 % des cas, la paralysie survint sur le membre vacciné.

Begünstigt Impfung die Entwicklung einer Poliomyelitis?

76 Fälle von Poliomyelitis wurden im St. Sophie-Kinderhospital während des Herbstes 1950 aufgenommen. Davon war in 17 Fällen eine Impfung mit gemischter Vaccine (Pertussis-Tetanus-Diphtherie) vorausgegangen. Das Intervall zwischen Impfung

und Auftreten der Paralysen betrug 2—14 Tage. In 75 % der Fälle trat die Lähmung im Bereich des Gliedes auf, an welchem geimpft wurde.

¿Puede la vacunación profiláctica favorecer el desarrollo de poliomielitis?

Sesenta y seis casos de poliomielitis fueron admitidos durante el año 1950 en el hospital de niños Santa Sofía. En diez y siete de ellos había previamente una historia de vacunación anterior con vacuna mixta (pertusis-tétanos-difteria). El intervalo entre la vacunación y la aparición de la parálisis fué de 2 a 14 días. En un 75 % de los casos la parálisis ocurrió en la pierna donde se había efectuado la vacunación.

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Psychogenic Obesity in Children. I

by TORBEN IVERSEN

Obesity in children is, in the final analysis, the result of a food intake which exceeds the amount expended for energy and growth. The problem to be considered here is to what extent this excessive food intake, possibly coupled with physical inactivity, in children may be caused by demonstrable psychologic factors.

This investigation was not based on any special training in child psychiatry and psychoanalysis. This implies that not all the conflict matter may have been elicited, and that no direct demonstration of the psychopathologic mechanism inducing the obesity and of any symbolic importance of the food intake has been possible. Accordingly, the conclusions must to some extent be discretionary and subjective.

The author has considered the possible psychogenic factors in a somewhat wider range than BRUCH has done. It was not tried exclusively to trace the specific family constellation and attitude of the mother.

As BRUCH drew her conclusions from a series of patients belonging to a special social class and further did not attach particular importance to the familial occurrence of obesity, some attention was directed also to these factors.

Method of Study

The series of patients comprised *40 children, 15 boys and 25 girls*, born during the years 1935—45. At the time of examination, in 1949, the boys were 6—14 years and the girls were 4—14 years old; 22 of the girls were 6 years or more.

All the patients had been admitted to or examined in Danish pediatric departments during the years 1947—49. Twelve of the children had been admitted to the *Pediatric Department, University Clinic at Rigshospitalet*, Copenhagen, 16 children to the *Dronning Louise's Children's Hospital*, Copenhagen, while the remaining 12 children had been examined in the *Endocrine Clinic* of the latter hospital.

Only children in whom obesity had been diagnosed without endocrine disorders were included in the series. No case had been diagnosed as FRÖHLICH's syndrome or dystrophia adiposogenitalis. None of the patients showed signs of hypothalamic or

other cerebral lesions. Patients with a basal metabolic rate lower than minus 15 per cent (calories per hour per square meter referred to age according to BIERRING's (1) and VOGELIUS' (4) Danish standards) were excluded. The intelligence of all the children was normal.

During the years under consideration 68 patients answered to the aforementioned requirements; but for various reasons, e.g. geographical conditions (Rigshospitalet takes patients from all parts of the country), uncooperative parents, and disease in the family, 28 of these patients were prevented from being examined. However, the remaining 40 patients must be considered to be a representative series comprising all social classes.

Hospital patients were selected to ensure that all had been subjected to a thorough clinical examination. Thus, apart from the 12 patients from the Endocrine Clinic, who had been examined on the initiative of the school doctors, the series consisted exclusively of children whose parents regarded the obesity as a disease requiring hospital treatment. On the other hand, the series is only to a slight extent representative of the presumably considerable number of obese children whose parents do not find treatment necessary. And since it was particularly the attitude of the parents which was subjected to investigation, the conclusions expressed in this paper can scarcely be said to apply to the causes of obesity in childhood as a whole.

The *information* originates partly from the case records and partly from interviews with the mothers during visits to the homes, arranged in order to obtain an impression of the family constellation and the environment. An attempt was made to make the mother disclose her attitude to the child and its obesity, and to find an explanation for this attitude in experiences from her own childhood and later life, particularly as far as her married life was concerned. Information about the child's personality and an exhaustive history of the child's life and psychologic influences was obtained. In play and interviews with the child it was tried to form an impression as to the child's personality and attitude to the obesity. Supplementary information was in some cases obtained from the fathers and other members of the family and from formmasters. Such psychologic tests as had been previously performed were utilized to a great extent.

A thorough critical *analysis* was made in *each individual case* with a view to psychologic factors. A case was classified as psychogenic obesity, if it was the impression that the food intake might be supposed to be of emotional significance to the child and (a) the child had been exposed to psychotraumatic experiences in the family or environment at the time before the development of the obesity, or (b) the child had revealed emotional and behavior problems (fear, anxiety reactions, etc.) or psychosomatic disorders (enuresis, abdominal pain, etc.) prior to the onset of the obesity, or (c) the child, on account of the maternal attitude, had been abnormally attached to the mother and isolated from social contact with other children.

In the *analysis of the whole series* special attention was directed to the frequency of such factors as in the opinion of BRUCH are typical of the environment of the obese child (size of the family, family position of the patient, attitude of the mother, etc.). Likewise it was examined how often the onset

of the obesity could be related to certain emotional occurrences in the child's life, such as beginning of school, birth of siblings, etc. From such summarizing information no conclusions can be drawn as to the etiology of the obesity in the individual case, although certain general conclusions may be justified in more comprehensive series.

A *control material* of non-obese children with regard to the attitude of the mother to the child and similar factors was not provided. The author takes support, inter alii, in the opinion expressed by KANNER (3): "Parental attitudes are not easily accesible to statistical evaluations. They are too complex for that, too variable in their manifestations. . ." In a sufficiently large series of normal children it will undoubtedly be possible to find a similar maternal attitude in some cases; but this only means that such an attitude does not invariably lead to obesity, without excluding that it may be of essential importance for the explanation of obesity in children. On the other hand, in families with more than one child it was attempted to find out whether the mother's attitude to the obese child was different from that shown to the other children in the family.

Likewise, the series under consideration was regarded as numerically too limited for a comparison with a normal material with regard to such factors as the number of children in the family, obesity in the family, etc.

Results

In *16 patients, 9 boys and 7 girls psychologic factors* according to the above mentioned criteria might be supposed to have been the important factor in the development of the obesity.

It must be pointed out that it was the interaction of several factors coinciding with the onset of the obesity that was decisive for the classification.

A short summary of the sixteen cases will be given below.

In the remaining *24 patients, 6 boys and 18 girls, psychologic factors* were *questionable or non-existent.*

The data of the 40 patients are presented in Table I.

In the following analysis of the total series the correspondent figures for the psychogenic cases are put in brackets.

Obesity in the Family.

One or both parents were or had been obese in 31 (12) cases, and in 26 (11) of these cases other members of the family were obese too. In 4 (2) cases there was no obesity in parents or other members of the family. A more detailed classification is illustrated by Table II.

TABLE I

Descriptive Data for the Individual Patients.

Case number	Sex	Age (years)	Position of child	Overweight per cent	Multiples of standard deviation	B.M.R.	Age at onset (years)	Obesity in Family				
								F	FF	M	MF	S
1[1]	B.	6	1/2	49	6.4		0	−	+	+	−	−
2	B.	7	1/1	31	4.0		4	−	+	−	+	
3	B.	8	3/3	103	10.7	− 5	3	−	+	+	+	−
4	B.	9	1/1	72	9.7	− 4	4	+		+	−	
5[1]	B.	10	1/2	31	4.4	− 7	3	−	−	−	−	−
6[1]	B.	11	1/2	10	1.0		8	−	+?	+	−	−
7	B.	11	1/2	29	2.9		7	+	+	+	−	−
8[1]	B.	11	1/1	39	4.2		8	+	+	+	+	
9[1]	B.	11	2/3	73	6.9	−13	5	+	+	+	+	−
10[1]	B.	12	2/2	29	3.1	+ 9	7	+	+	+	+	−
11[1]	B.	12	3/3	44	4.6	−11	7	−	−	+	−	+
12	B.	13	1/2	29	2.7	−13	10	+	+	+	+	−
13	B.	13	3/3	33	3.4	− 9	0	−	+	−	−	+
14[1]	B.	13	1/1	25	2.2		6	−	+	−	+	−
15[1]	B.	14	2/2	55	4.9		6	+	+	+	−	−
16	G.	4	1/1	20	2.4	− 2	0	+	−	−	−	
17	G.	5	2/4	25	3.4	− 1	0	+	−	−	−	−
18	G.	5	1/1	31	4.1	− 4	1	−	+	−	+	
19	G.	6	1/3	21	2.8		0	−	−	+	+	−
20[1]	G.	6	2/3	35	4.1	− 5	2	+	+	−	+	+
21	G.	8	2/2	79	9.9	+ 2	2	+	−	−	−	+
22[1]	G.	8	1/2	42	4.7		3	+	+	−	−	−
23[1]	G.	9	1/1	19	1.8		5	−	+	+	+	
24	G.	9	2/3	38	4.1		0	+	+	+	−	−
25	G.	9	2/3	33	3.7		3	−	−	+	+	−
26	G.	10	2/2	38	3.3		0	+	+	−	+	+
27	G.	11	1/1	20	2.3	− 6	2	−		−	−	
28[1]	G.	11	1/3	38	3.9	+ 5	7	−	−	+	+	+
29	G.	11	1/1	35	3.1	− 1	0	−	+	+	+	
30[1]	G.	11	1/1	37	3.6		7	−	+	−	+	
31[1]	G.	12	2/3	46	5.0	+ 2	7	−		−	−	−
32	G.	12	2/3	12	1.2	+ 3	10	+	+	−	−	−
33[1]	G.	12	1/2	32	2.7	−12	0	+	+	+	−	−
34	G.	12	2/2	20	1.7		0	+	+	−	−	−
35	G.	13	1/3	31	2.3	− 8	0	+	+	+	+	−
36	G.	13	1/1	33	2.7	− 6	9	+	+	+	+	
37	G.	13	1/2	80	6.3	−14	0	+	−	+	+	−
38	G.	13	2/2	32	2.5	+ 8	7	−	−	+	−	−
39	G.	14	1/2	33	2.9	− 3	11	−	−	−	−	−
40	G.	14	1/1	68	5.0	− 8	10	+	+	+	−	

[1] Psychogenic cases. As to *age* of the patient, the figures refer to 1949, when the investigation was made. In the figures expressing *position of child* stillborn, dead children, and half-siblings are excluded. The *degree of overweight* is calculated according to BROMAN, DAHLBERG & LICHTENSTEIN's height-weight tables. The figures expresses the percentual overweight and multiples of the normal standard deviation. *The basal metabolic rate* is calculated according to BIERRING's and VOGELIUS' standards. *Age at onset:* 0 = during first year of life. *Obesity in family.* F: father, M: mother. FF and MF: obesity at least in one of the father's respective mother's parents or siblings. S: sibling.

Table II

Obesity in Family.

	F and M + Fam.	F or M + Fam.	F or M − Fam.	− F − M + Fam.	− F − M − Fam.
Total series					
Boys 15	7	3	1	3	1
Girls 25	6	10	4	2	3
Together 40	13	13	5	5	4
Psychogenic cases					
Boys 9	4	2	1	1	1
Girls 7	1	4	0	1	1
Together 16	5	6	1	2	2

F: father, M: mother. Fam.: obesity at least in one of the father's or mother's parents or siblings.

Table III

Degree of Obesity.

	Percentual overweight		
	Less than 40	40 to 70	More than 70
Total series			
Boys 15 . .	9	3	3
Girls 25 . .	20	3	2
Together 40 . .	29	6	5
Psychogenic cases			
Boys 9 . .	5	3	1
Girls 7 . .	5	2	0
Together 16 . .	10	5	1

The degree of overweight is calculated according to Broman, Dahlberg & Lichtenstein's height-weight tables.

Table IV

Age at Onset of Obesity.

	Years of age			
	0—2	3—5	6—8	9—11
Total series				
Boys 15 . .	2	5	7	1
Girls 25 . .	14	3	4	4
Together 40 . .	16	8	11	5
Psychogenic cases				
Boys 9 . .	1	2	6	0
Girls 7 . .	2	2	3	0
Together 16 . .	3	4	9	0

Degree of Obesity.

The average overweight of the series at the first observation in hospital was, according to BROMAN, DAHLBERG & LICHTENSTEIN's height-weight tables (2), 39 (38) per cent, namely 48 (39) per cent in the boys and 36 (36) per cent in the girls. The maximum overweight for boys was 103 (73) per cent and for girls 80 (46) per cent. The distribution of the series according to the degree of obesity is shown in Table III.

Age at Onset of Obesity.

In 16 (3) cases the patient had become obese during the first 3 years of life. Further 5 patients had been slightly obese since the first years, but as the obesity only became strongly accentuated at a later period, these patients are included in the following groups. 8 (4) patients developed obesity at 3—5 years of age, 11 (9) patients at 6—8 years, and 5 (0) patients at 9—11 years of age. The classification of the series in relation to the age at onset of obesity is presented in Table IV.

Size of Family and Family Position of the Patient.

The series comprised 12 (4) only children. Fifteen (7) of the families had two children, 12 (5) families had three children, and 1 (0) family had four children. In these figures stillborn, dead children and half-siblings are excluded. In families with more than one child the patient was the oldest child in 12 (6) cases and the youngest in 9 (3) cases. The average number of living children per family was 2.0 (2.1).

Mother's Attitude to the Child.

A nonrejecting overprotection of the child was observed in 20 (15) cases. A rejecting attitude of the mother was traced in 3 (0) cases, and in 1 (1) case an overprotective attitude had been replaced by rejection.

In 6 families with two children of whom the patient was the older the mother showed an overprotective attitude to the patient in 5 (4) cases, but hardly to the second child. In all six cases the patient was cowed and subdued by the younger sister or brother.

Four mothers continued nursing the child for more than 12 months; in 2 (1) cases breast feeding was not discontinued until the child was two years old.

According to the statement of the mothers, the child was unwanted in 12 (1) cases, and in 3 (0) of these marriage had been contracted because she was pregnant.

The following factors may have contributed to the attitude of the mothers:

Mother's Childhood. 14 (4) mothers described their childhood as unhappy; 8 (2) of these spoke of "lack of love," "strict upbringing," "no confidence," etc., 3 (1) had been educated by foster-parents, and in 3 (1) cases the homes had been very poor.

Parental Relationship. Incompatibility and lack of harmony between the parents were stated in 11 (5) cases; in 5 (3) of these the marriage had been dissolved. In 2 (0) cases the child was illegitimate, and the mother had not subsequently cohabited with the father. In 2 (1) cases the father was dead. A domineering attitude of the mother coupled with weakness and subservience of the father was found in 7 (4) cases.

Age of Mother. In 6 (2) cases the mother was 36 years or more at the birth of the patient, and in 3 (1) of these the patient was the oldest or at least the oldest living child of the marriage.

Stillborn and Dead Children. Prior to the birth of the patient 2 (1) mothers had had a stillbirth. Eight (3) mothers had lost a child, and in 7 (3) of these cases the patient had been the next child of the marriage. Three (1) of these children had been obese since the first year.

Psyche of the Children.

Varying degrees of emotional disturbances or difficulties of adjustment were recorded in 26 (16) patients. Twenty-two (10) children, 10 (5) boys and 12 (5) girls, displayed an excessive affection or prolonged dependence upon the mothers.

Thumb sucking or nail biting were present in 13 (4) cases, and tics in 5 (4) cases. Seven (4) of the patients either suffered or had suffered from nocturnal enuresis and 5 (3) from sleeping disturbances.

The obesity had been preceded by enuresis in 3 (2) cases, by abdominal pain in two cases, and by tics and sleeping disturbance in 1 (1) case.

Development of Obesity in Relation to Various Emotional Experiences.

Birth of Sibling. Nine of the patients were not obese when a sister or brother was born. In 4 (4) patients obesity developed within the year following the birth of a sibling.

Dissolution of Parents' Marriage. In 3 (3) patients the obesity began after the divorce of the parents, and in 1 (0) patient it further increased.

Beginning of School. In 9 (7) patients the obesity started at 6—8 years of age. A complaint of word blindness was present in 3 (2) of these cases. In 2 (2) patients who had been moderately obese from the first years, the obesity increased when they began school.

Adenotomy and Tonsillectomy. In 4 (2) patients obesity developed within a year after adenotomy and/or tonsillectomy.

Case Reports

(Summary of the sixteen cases of psychogenic obesity)

CASE 1. *Boy*, 6 years old, the older of two children. Obesity from his first years of life. The mother is strongly overprotective, probably because she has given birth to a still-born child previous to the birth of the patient. For three years after that she dared not try to have another child for fear that the child should also be still-born. She nursed the child for two years. Even now the mother is much anxious about the child. He is scared and shy and he is inhibited and subdued by his 3-year-old sister. He has had tics from 5 years of age.

CASE 5. *Boy*, 10 years old, the older of two children. Obesity at 3 years. The mother is clearly overprotective and always apprehensive for the child. His birth was difficult. At two years he was seriously ill with tonsillitis. "He hardly eat for five days, and we thought we should lose him." Until he was about three years he had frequent vomitings, but the mother gorged him, "so that he shouldn't fade out." After that his obesity began. He has always been very timid and cautious. When he got a bicycle, which he had wanted for a long time, he dared not ride on it. He sucked his fingers till he was about six years old. Now he bites his nails and has tics. He is subdued by his 6-year-old sister.

CASE 6. *Boy*, 11 years old, the older of two children. Obesity at 8 years. The parental relationship has always been bad. The mother is attached to the boy to an abnormal extent. Earlier he had a period with poor appetite, and the mother had to "tempt and stuff the food down his throat." When he started school, he was nervous, had tics, and could not sleep. His obesity developed during the following year. A Rorschach test at 10 years showed signs of insecurity, egotism, and instable affections. He is dominated by his 9-year-old brother.

CASE 8. *Boy*, 11 years old, only child. Obesity of low degree from his first years of life. He was born when the parents had been married for thirteen years. The birth was difficult. At that time the mother was 38 years old. Breast feeding only stopped because the mother was sent to hospital, at which time the child was 18 months. The parents have always been very overprotective. The mother was anxious about him and completely isolated him until he began school. Before that time his appetite was poor, then his obesity rapidly developed. Till he was about ten he was attached to the mother, of whom he loved to be fondled by, then he turned cross and disobedient. A Rorschach test at 11 years showed signs of insecurity, anxiety, infantilism, and strong contacting urge.

CASE 9. *Boy*, 11 years old, the second of three children. Obesity at 5 years. The parents got on badly. The father was oversexed and addicted to drinking. The mother has always spoilt the boy "in order to substitute the father to some extent." At 3 years the boy attended a fight between the parents. They were divorced when he was four. From the age of five he was forced to visit the father; after each visit he had abdominal pain, and at the same time he began to gain in weight. A psychiatric examination at 10 years showed a shy and timid boy.

CASE 10. *Boy*, 12 years old, the younger of two brothers. Obesity at 7 years. The father is periodic inebriate, which has threatened his married life. The boy has always been lonely; he was "rather like a baby when he started school." His obesity began shortly after. He had difficulties on account of word blindness. At 8 years enuresis

began. He feels depressed because of the father's drinking-habits. He is inhibited and subdued by his 18-year-old brother.

CASE 11. *Boy*, 12 years old, the third of three children. Obesity of low degree from his first years of life. The mother was 40 when he was born. She has always been much concerned about him. In infancy he was in hospital for two months with pneumonia. When dismissed, the doctors are said to have declared that "he could not gain in weight," so the mother decided that "he should have all the food that he could eat." He bit his nails before he started school. Then his obesity increased. He suffers from word blindness. He feels lonely, is shy and dependent on his mother.

CASE 14. *Boy*, 13 years old, only child. Obesity at 6 years. The mother is typically overprotective and much attached to the child. The first child, a girl, when 7 years old died of diphtheria. The mother thinks that this "need not have happened," she has had "bad nerves ever since." When he was a baby the mother had to "struggle with him to make him eat." He has always been lonely and "very cautious." Obesity began when he started school. His schoolmates teased him, so he used to cry every morning before going to school. He has tics. He is rather girlish and very dependent on the mother.

CASE 15. *Boy*, 14 years old, the younger of two children. Obesity at 6 years. Because of frequent illness during his first years of life he was overprotected by the mother. He was "more coddled than his brother." In early childhood he was anxious at night. Until he was six he had frequent vomitings, then obesity began. A Rorschach test at 13 years showed signs of infantilism, which may particularly be directed to the mother.

CASE 20, *Girl*, 6 years old, the second of three children. Obesity at 2 years. The mother is depressive and suffers from sexual neurosis, the father is oversexed. The parents do not get on well. The mother feels particularly attached to this child, as the father deserted her after the birth of the child. The child is very fond of her mother, but she is frightened and has adjustment difficulties to other children. So the mother keeps her at home and isolates her from other children. If the mother refuses to give her food, she cries and helps herself.

CASE 22. *Girl*, 8 years old, the older of two children. Obesity at 3 years. The parents were divorced when the child was three. She had always loved her father, but the mother did not allow her to see him after the divorce. She has had sleeping disturbances from the age of two. The obesity began after the divorce of the parents. At that time the mother became much attached to her, and now the child is very dependent on her. She gets "miserable," if the mother refuses to give her food. She is very "nervous" and scared.

CASE 23. *Girl*, 9 years old, only child. Obesity at 5 years. The mother was divorced from her first husband when the child was four. The mother had to sleep with the child every night at the time before the divorce, as the husband had threatened to kill them. During the following year the child's obesity began. She is nervous, has troubled sleep, and has suffered from enuresis from the age of seven. She craves her mother's love and misses her real father, whom she visits. The mother has been married to her second husband for two years.

CASE 28, *Girl*, 11 years old, the oldest of three children. Obesity at 7 years. The first child died one month old on account of "an open back." The mother was "wild with

despair" and feared that the next child should be born with a deformity, too. The child is nervous and anxious after having been subject to a bite from a dog, a road accident, and an air-raid warnings. From 5 years of age she has suffered from enuresis and at 7 she developed obesity. She is still "nervous."

CASE 30. *Girl*, 11 years old, only child. Obesity at 7 years. The mother is depressive; she has always spoilt the child. Mother and child were attached to the mother's parents, who died when the child was seven. Enuresis began at 4 years and obesity at 7 years of age. She suffers from word blindness and has difficulties of adjustment to other children. At home she is reticent and timid.

CASE 31. *Girl*, 12 years old, the second of three children. Obesity at seven years. The father is often intoxicated. The child was unwanted. However, the mother has always been much attached to the patient and apprehensive about her. She has always been very childish. From 7 years she has suffered from bronchial asthma and abdominal pain followed by obesity. She has been greatly exhausted by the asthma. She still gets abdominal pain, and recently also headache, when she is nervous.

CASE 33. *Girl*, 12 years old, the older of two children. Obesity from her first years of life. The father died when the child was five. She is a "substitute" for a girl who died of meningitis two years old. The mother used to spoil her before the father died, but since then she has neglected her. The child has always been jealous of her brother, who was born when she was five. She is scared, has difficulties in contacting other children, and she seeks refuge in isolation. She is "always in the pantry." The mother thinks that the child eats so much because she considers herself neglected.

Comment

It is to HILDE BRUCH's credit to have called attention to the importance of psychologic factors in the aetiology of obesity in children. In a series of 40 obese children BRUCH could point to a special family constellation and maternal attitude, which in BRUCH's opinion explained the obesity of the children.

In the present series of 40 obese children, 15 boys and 25 girls, psychogenic factors were ascertained in 16 children, 9 boys and 7 girls. In 13 boys the obesity had developed after the first three years of life; in 8 of these the obesity could be related to psychologic factors. In 11 girls the obesity had begun after the first three years, psychologic factors being ascertained in 5 of these children.

The maternal attitude to the child, described by BRUCH, practically corresponds to KANNER's "compensatory overprotection." The typical attitude found in the present series, however, corresponded to KANNER's "nonrejecting overprotection" expressive in an exaggerated solicitude for the child. And it was not the impression that this attitude showed itself in overfeeding the child. Thus, no ambivalent attitude could be proved. It may be presumed that a psychoanalytic inquiry is necessary in that respect.

The family constellation described by BRUCH was only found occasionally in this series.

A great many of the children were very dependent on the mother, and more than half of the children showed signs of emotional instability. In some cases these conditions were presumably due to the same causes as those that brought about the obesity; in other cases they were most likely produced by the difficulties raised by the obesity.

BRUCH is of opinion that the obesity reaction is due to the fact that the child's "previous experiences had endowed eating and social activities with a special emotional significance." In the present series, however, obesity occurred in most of the obese children's families. There was no certain difference between the frequency of family obesity in the psychogenic cases and the non-psychogenic ones.

It may be *concluded* that psychogenic factors — probably superimposed constitutional factors — are important in certain obesity cases in childhood. HILDE BRUCH's theory, however, seems to be too specific.

Summary

40 obese children, 15 boys and 25 girls, 4—14 years of age, were examined with a view to psychogenic factors.

The children had been admitted to the Pediatric Department, University Clinic at Rigshospitalet, Copenhagen and to the Dronning Louise's Children's Hospital, Copenhagen.

Psychogenic factors were ascertained in 16 children, 9 boys and 7 girls. In 13 of these children, 8 boys and 5 girls, the obesity had developed after the first three years of life.

In the remaining 24 children, 6 boys and 18 girls, psychogenic factors were questionable or non-existing. In 13 of these children, 1 boy and 12 girls, the obesity had begun during the first three years of life.

A nonrejecting maternal overprotection was disclosed in 20 cases.

Varying degrees of emotional disturbances or difficulties of adjustment were recorded in 26 cases.

Obésité psychogène dans l'enfance. I.

Quarante enfants obéses, 15 garçons et 25 filles, de 4 à 14 ans, ont été soumis à un examen, en vue de rechercher les facteurs pscyhogènes. Les enfants ont été admis au Département pédiâtrique de la Clinique Universitaire, Rigshospitalet à Copenhague, et à l'Hôpital d'Enfants Dronning Louise à Copenhague. Des facteurs psychogènes ont été constatés chez 16 enfants, 9 garçons et 7 filles. Chez 13 d'entre eux, 8 garçons et 5 filles, l'obésité s'est développée après les trois premières années de la vie. Chez les 24 autres enfants, 6 garçons et 18 filles, des facteurs psychogènes étaient douteux ou absents. Chez 13 de ces enfants, 1 garçon et 12 filles, l'obésité a commencé durant les trois premières années de la vie. Une "surprotection" maternelle non rejetée s'est révélée dans 20 cas. Des degrés variables de troubles émotifs ou de difficultés d'adaptation ont été observés dans 26 cas.

Über psychogene Fettsucht bei Kindern. I.

Vierzig fette Kinder, 15 Knaben und 25 Mädchen von 4—14 Jahren wurden in Hinblick auf psychogene Faktoren untersucht. Die Kinder waren der pädiatrischen Abteilung der Univ. Klinik in Rigshospitalet und dem Dronning Louise's Kinderhospital zu Kopenhagen überwiesen worden. Psychogene Faktoren wurden bei 16 Kindern, 9 Knaben und 7 Mädchen gesichert. Bei 13 dieser Kinder, 8 Knaben und 5 Mädchen, hatte sich die Fettsucht nach dem 3. Lebensjahr entwickelt. Bei den restlichen 24 Kindern, 6 Knaben und 18 Mädchen, lagen psychische Faktoren nicht vor oder waren fraglich. Bei 13 dieser Kinder, einem Knaben und 12 Mädchen, begann die Fettsucht in den ersten 3 Lebensjahren. Eine mütterliche Überbegünstigung wurde in 20 Fällen nachgewiesen. Verschiedene Grade von emotionellen Störungen oder Schwierigkeiten im Einordnen wurden in 26 Fällen registriert.

Sobre la obesidad psicogénica en la infancia. I.

Se ha examinado a 40 niños obesos (15 niños y 25 niñas) de edad entre 4 y 14 años, en vista a los factores psicogénicos que pudiera haber en su origen. Estos niños habían sido admitidos en el Departamento Pediátrico de la Clínica Universitaria Rigs-Hospital de Copenhague y del Hospital de niños Louise Dronning también de Copenhague. Factores psicogénicos podían establecerse ciertamente en 16 niños (9 niños y 7 niñas). En 13 de estos enfermos (8 niños y 5 niñas) la obesidad se había desarrollado después de los tres primeros años de la vida. En los restantes 24 niños (6 niños y 18 niñas) la existencia de factores psicogénicos era dudosa o inexistente. En 13 de estos enfermos (1 niño y 12 niñas) la obesidad había empezado durante los tres primeros años de la vida. Una no rechazada sobreprotección de la madre se descubrió en 20 casos. Diversos grados de disturbios emocionales o dificultades de adaptación se encontraron en 26 casos.

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Incidence of Rh Antibody Formation in First Pregnancies

Outcome of Pregnancies in 23 Cases not Previously Sensitized to Rh Antigens

by OTTO HARTMANN and O. J. BRENDEMOEN

It is still uncertain how often Rh immunization develops in the course of a first pregnancy. DIAMOND (1) and MOLLISON (3) consider that it is rare; but these are estimates, and definite knowledge on this point is needed because if the incidence were actually very low, routine testing for Rh antibodies in Rh negative primigravidae would be unnecessary. Recently VAN LOGHEM (2) found that among 870 Rh immunized pregnant women 70, or 8 per cent, were primigravidae; 5 of these 70 had a history of previous blood transfusion.

Nowadays more than 90 per cent of all pregnant women in this country have a serological test for syphilis; most of these tests are made in this laboratory and the blood samples received are also tested for the Rh factor. A series of about 75,000 pregnant women have been included in this study.

Most samples are obtained early in pregnancy by a local practitioner or at an ante-natal clinic. A few are obtained when the patient is admitted to a maternity hospital. If the woman is Rh negative (D negative) a blood sample from the husband is also requested. If the husband is Rh positive or if a sample from him cannot be obtained, a further test for antibodies is done on the woman after the 36th week of pregnancy. There is little possibility of selection in this series. The women who are not tested are those who do not seek medical advice during pregnancy and who are delivered in their home — a practice which persists only in the more remote rural districts.

The frequency of D negative women was slightly more than 15 per cent and of these, 520 or about 5 per cent had developed antibodies; this 5 per cent includes 63 women who had apparently been sensitized by transfusion with Rh positive blood.

We have classified as first pregnancies, only those in women who have never (as far as they knew) received a blood transfusion or an injection of blood. We have also excluded the women with a previous history of abortion. Table 1

TABLE 1.

Frequency of Rh immunization found by routine testing of about 75,000 pregnancies.

Immunization by transfusion	63
Immunization by 1st pregnancy (no transfusion)	23
Immunization by repeated pregnancies (no transfusion)	434
Total immunized	520

shows that in the primigravidae group, there were 23 women who possessed Rh antibodies. It is possible that some of these women might have concealed information of previous abortions or pregnancies, but this is unlikely, because nearly all the 23 women claimed that they wanted a child and as soon as they understood that the questions we asked were important for the well being of their unborn child, they answered all our questions readily. Although 63 patients gave a history of previous blood transfusion, none admitted to injections of blood — suggesting that injections of blood are rarely used in this country.

Information about the outcome of the pregnancies was obtained either from the maternity hospitals, or from the physician attending the infant, or from the mothers themselves. The results are shown in Table 2, which includes the month of gestation in which the Rh testing was made, and the antibody titre in 20 per cent bovine albumin medium.

In these 23 women, there were three still births, and four babies who required treatment. One of these babies died. The 19 survivors are all known to be alive and without neurological sequelae of erythroblastosis. The correlation between the Rh antibody titre and the severity of haemolytic disease is very high. Only in one case (Case 11) was there a high antibody titre without clinical manifestation of haemolytic disease in the infant.

Conclusion

In this series of Rh immunized women, 5 per cent of immunizations developed in the course of a first pregnancy and previous blood transfusions or abortions does not account for these immunizations. 7 infants were seriously affected and 4 died, that is, one third required treatment and nearly one fifth of the infants died. This shows that Rh immunization in the course of a first pregnancy is commoner than usually believed, and that routine testing for the presence of antibodies during the course of a first pregnancy in a Rh negative woman is not only justified but desirable.

TABLE 2.

Outcome of 23 Rh immunizations in first pregnancy.

(The figures in the table are the Rh antibody titers in 20 % bovine albumin, shown in the period when tested. B = date of birth. * not titrated, † titrated at birth)

		Weeks of gestation						Clinical result and/or treatment
		0–12	13–24	25–32	33–36	37–38	39–40	
				Stillborn				
Died	1					512 B		Stillborn, macerated
	2					512 B		» » » »
	3	0			512 B			» » » »
				Treated				
	4				B*			Transfused, died
	5	0				64	128 B	Exchange transfused
	6						B † 128	Transfused
	7				1024		1024 B	Exchange transfused
				Not treated				
	8		0			2	64 B	Anemia
	9			0		32	32 B	Icterus
	10					4	B	Normal
	11			0		128	B	»
	12			4		8	B	Not observed
	13				0	4	B	» »
	14		0			2	B	Normal
	15				2	2	B	»
	16			2		2	B	»
	17						B † 32	»
	18						B † 4	»
	19						B † 2	Icterus
	20						B † 16	Normal
	21						B † 4	Icterus
	22						B † 8	Normal
	23						B † 4	»

Alive, without sequelae

Summary

In a series of about 75,000 unselected pregnancies, 520 were found to have Rh antibodies. 63 of these patients had received blood transfusions. 457 had apparently been sensitized by pregnancy alone, and of these, 23 or 5 per cent were primigravidae. Serious haemolytic disease occurred in 7 of the infants born to these mothers, and 4 died. Routine testing for Rh antibodies in Rh negative primigravidae is therefore desirable.

Fréquence de la formation d'anticorps Rh durant la première grossesse.

Sur une série d'environ 75 000 femmes enceintes non sélectionnées, on en trouve 520 possédant des anticorps Rh. 63 des patientes ont reçu des transfusions sanguines.

457 ont été apparement sensibilisées uniquement par grossesse, et parmi celles-ci, 23 ou 5 % étaient primipares. Une maladie hémolytique grave est survenue chez 7 des nourrissons nés de ces mères, et 4 sont morts. Un test de routine pour recherche des anticorps Rh chez les primipares Rh négatif est donc désirable.

Häufigkeit der Rh-Antikörperbildung bei der ersten Schwangerschaft.

In einer Serie von etwa 75 000 nicht ausgesuchten Schwangerschaften wiesen 520 Rh-Antikörper auf. 63 von diesen Patientinnen hatten Bluttransfusionen erhalten. 457 wurden offensichtlich durch die Schwangerschaft allein sensibilisiert und von diesen waren 23 = 5% Erstgebärende. Schwere hämolytische Erkrankungen traten bei 7 der von diesen Müttern geborenen Kindern auf, 4 starben. Routinetestungen auf Rh-Antikörper bei Rh-negativen Erstgebärenden sind deshalb wünschenswert.

Incidencia de la formación de anticuerpos Rh en el primer embarazo.

En series de aproximadamente 75 000 embarazos no seleccionados, en 520 se encontraron anticuerpos Rh. 63 de estas pacientes habían recibido transfusiones de sangre. 457 habían sido sensibilizadas aparentemente únicamente por el embarazo y de éstas 23 o sea 5 % eran primiparas. Una enfermedad hemolítica de tipo severo apareció en 7 de los niños nacidos de estas madres y de ellos 4 fallecieron. La investigación de rutina de los anticuerpos Rh en las primiparas Rh negativas es aconsejable.

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Coeliac Disease

I. *Criticism of the Various Methods of Investigation*

by H. A. WEIJERS and J. H. VAN DE KAMER

Introduction

In diseases which are characterized by the occurrence of steatorrhoea, caused by a disturbed fat absorption or by a disturbance in fat-digestion, — e.g. coeliac disease, sprue, pancreatic fibrosis etc. — the following methods of investigation are generally used.

The amount of fat present in the faeces is determined, from which is calculated what proportion of dietary fat has been absorbed (coefficient of absorption, C. A.), or an attempt is made to gain an impression of the fat absorption from the degree of lipaemia, or from the vitamin A tolerance curve.

Determination of fat absorption by examination of faeces

a) Microscopic examination

In many clinics it is customary to form an opinion on the degree of fat absorption from microscopic observations of the fat in the faeces. This method is very simple. The correctness, accuracy and reproducibility of this method, however, leave very much to be desired! This is plainly shown when the results of microscopic observations are compared with those of chemical determinations, as can be seen in figure 1.

This figure shows the impossibility of making a reliable estimate. In the extreme cases, 0—3 % and > 9 % fat, 60 to 70 % of the observations agreed with the chemical determination as to the fat content; in the case of fat con tents of 3—9 % this agreement is only about 40 %. Moreover, the differentiation "much," "medium" and "little" is certainly not very precise. FRAZER and many others have come to the same conclusion.

Even in cases where the fat content is correctly estimated, we may not draw conclusions regarding the degree of absorption on the basis of this value

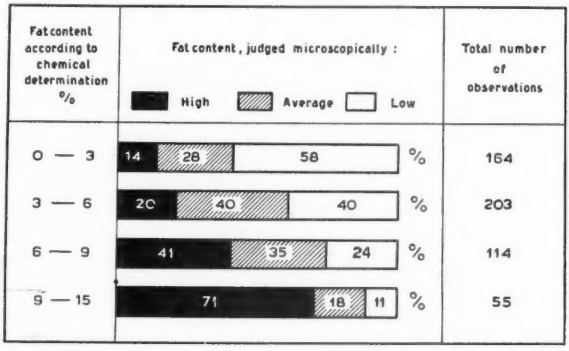

Fig. 1. Fat content of faeces, determined chemically and microscopically.

only. In fact, the amount of excreted fat is not determined by the *fat content* of the faeces only, but just as much by the *quantity* of faeces. The microscopic observations never take the amount of faeces into account, however.

b) Chemical investigation

1. The fat-content of faeces expressed in percentage of wet and dry substance

It is indeed possible to determine exactly the fat content of the faeces by chemical analysis. However, conclusions cannot be drawn as to the degree of fat absorption from this analytical result alone, as in this case also the *quantity* of faeces is not taken into account.

This is shown by the correlation figure (fig. 2), in which the fat content of wet faeces is plotted against the percentage of dietary fat which has actually been absorbed (coefficient of absorption).

It appears that with *each* percentage of absorbed dietary fat, one can come across faeces in which the *fat content* varies from 1—25 %. It must be emphasized that even low fat contents (1—5 %) can correspond with very differing coefficients of absorption.

However, when the amount of faeces excreted per 24 hours was always the same, it could be seen that good correlation existed between the coefficient of absorption and the fat content of the faeces. The variation in the weight of the faeces might well be caused in the first place by the irregular secretion of moisture. In order to eliminate this factor, the fat content was expressed as percentage of dry matter. It now indeed appears that with normal people some correlation exists with the coefficient of absorption, as is shown in fig. 3.

This correlation is caused by the fact that the amount of dry substance excreted by normal people per 24 hours, is practically constant.

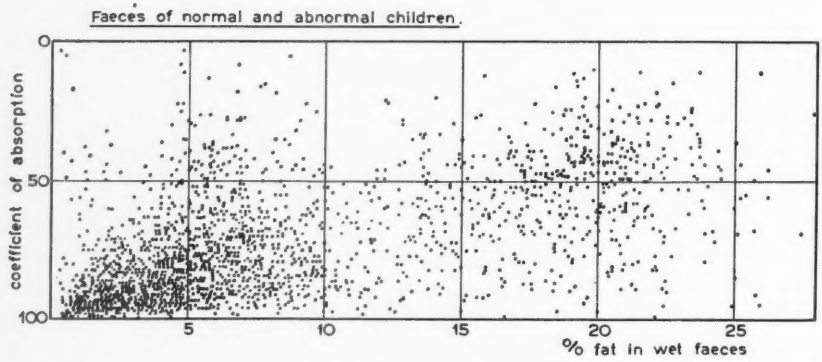

Fig. 2. Correlation of the coefficient of fat absorption and the fat content of the wet faeces (determined chemically).

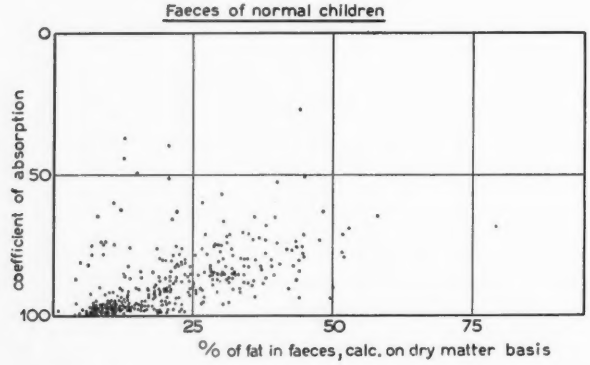

Fig. 3. Correlation of the coefficient of fat absorption and the percentage of fat in the faeces (calculated on the dry substance) in normal children.

In the case of persons with faulty absorption, no correlation appears to exist between the fat content of the faeces expressed as percentage of dry substance and the coefficient of absorption (see figure 4).

This is caused by the fact that the amount of dry substance excreted per 24 hours is dependent on the nature of the absorptive defect, on the composition of the diet and on the conditions under which the patients exists.

2. The coefficient of fat absorption

The determination of the coefficient of absorption, expressed in percentage, is a good method by which to obtain an assessment of fat absorption:

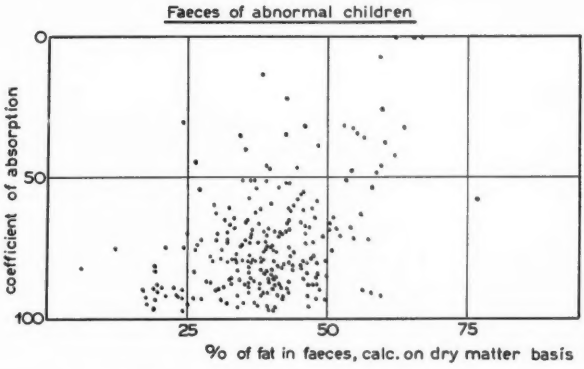

Fig. 4. Correlation of the coefficient of fat absorption and the percentage of fat calculated on the dry substance in children with steatorrhea.

$$\frac{g \text{ ingested fat} - g \text{ excreted fat}}{g \text{ ingested fat}} \times 100$$

The method for the determination was that of VAN DE KAMER—TEN BOKKEL HUININK—WEIJERS, by which the fat content of faeces can be rapidly and simply determined.

In order to collect the 24 hours' quantity of faeces from babies, the following method was used, for which no special material is necessary, while the faeces can be collected entirely free from urine. Put a piece of taffeta about 15 cm wide one side of an ointment jar with curved-over rim[1], diameter 8—10 cm (depending on size of buttocks). Fasten this by tying two strips of gauze-bandage round the jar; see that two loose ends of about 50 cm are left over on the side of the jar opposite the taffeta, and on the other side two loose ends of about 40 cm (see figure 5). Spread out a napkin folded three-cornerwise on a cot with the apex towards the foot, placing the jar in the middle with taffeta towards the head. Next place the child on the jar so that this just encloses the buttocks. Let a nurse press on the child's knees to prevent the jar from overbalancing and to keep it flat on the napkin. Take care that the jar fits well in front (in case of girls use a piece of cotton-wool to effect this). Place a layer of cotton-wool round the abdomen and loins and attach the jar by fastening the two strips on the side of the taffeta round the abdomen. Put a layer of cotton wool in both groins and let the nurse, who is still pressing the knees down, hold this cotton wool in place. Take the two front strips via the groins to the back, cross and tie on the abdomen. See that the taffeta lies flat against the back. The nurse must now place a rolled-up napkin (about 20 cm wide) under the legs and press it against the jar. Next place a piece of absorbent paper (about 30 cm long and 10 to 15 cm wide) lengthwise under the penis. Place the penis in a wide-mouthed bottle and fold the absorbent paper back over the bottle, wrapping the end round the neck. (For a girl use a very wide-mouthed bottle and an extra quantity of absorbent paper also putting supports under the head

[1] "Société Céramique" Maastricht (Netherlands).

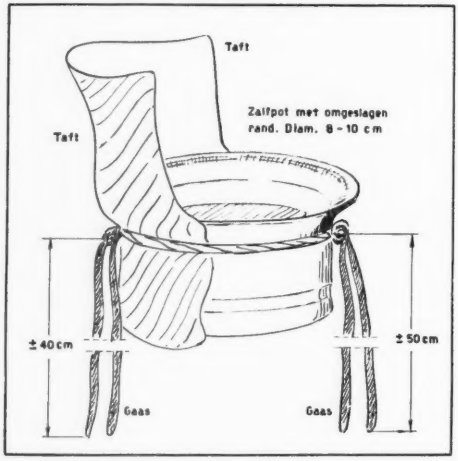

Fig. 5. Ointment jar used to collect faeces.

of the cot). Fasten the napkin firmly by bringing the lowest point to meet the other two points in the middle and secure by a safety-pin. Put a small pillow under the head and a rolled-up napkin under the lions so that the child's back is supported. Place a napkin, folded as a cravat, under the mattress and pin this fast over the child's knees. If necessary, place a flat pillow under the feet.

The above-described method can be used until the child has reached the age when the faeces can be collected in the normal way. With children below 6—8 months this method can, if necessary, be applied for some months. For children from 8 months to 1 1/2 years, who spend more of their waking-hours sitting than lying, the method should not be used more than is absolutely necessary.

The following deals with the *interpretation* of the C. A.

Through irregular defaecation and irregular passage through the intestines, a false picture is given when the C. A. is plotted graphically. This is eliminated by calculating the sliding mean of the C. A., e.g. for Wednesday the sum of the C. A.'s for Tuesday, Wednesday and Thursday, divided by 3; for Thursday the sum of the C. A.'s for Wednesday, Thursday and Friday, divided by 3, and so on.

It may be true that in calculating the sliding mean, a few variations in the true fat absorption may also be partly eliminated; it is certain, however, that the disturbing influence of nonessential variations is cancelled, which fully counterbalances this (TEGELAERS).

When we wish, on the basis of C. A.-determinations, to find out if the fat absorption in a certain period is better or worse than in another period, a statistical evaluation of the data obtained is necessary. This will the more readily give a significant difference, the more determinations have been made

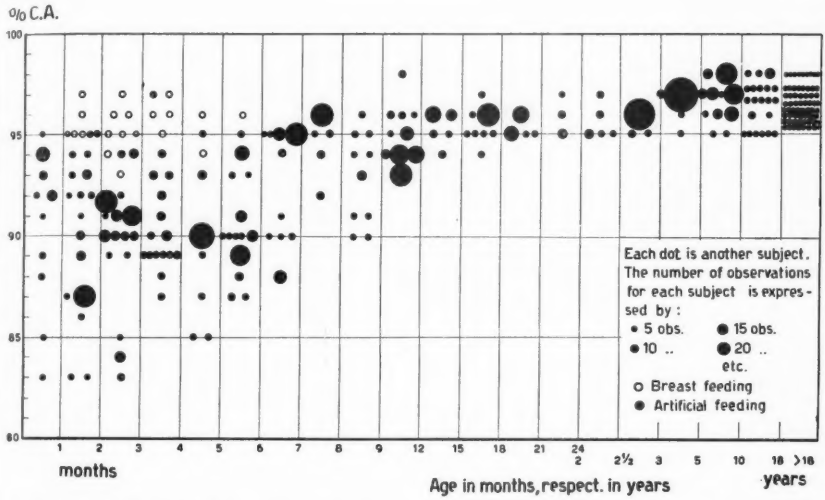
% C.A.
100
95
90
85
80
Each dot is another subject. The number of observations for each subject is expressed by :
• 5 obs. ● 15 obs.
● 10 .. ● 20 ..
etc.
o Breast feeding
● Artificial feeding
1 2 3 4 5 6 7 8 9 12 15 18 21 24
2 2½ 3 5 10 18 >18
months
Age in months, respect. in years
years

Fig. 6. Coefficients of fat absorption in normal babies, toddlers, children and adults.

in the periods. For this reason the C. A.'s were always determined *daily*. For the determination of a C. A. of about 95 %, a minimum of 3 consecutive observations is necessary; for C. A.'s of 90 %, 85 %, etc., relatively more; even many more the greater the deviation of the different observations.

By using the test of FISHER, it proved to be possible to compile tables from which could be fairly accurately seen how long a period must be used in order to call a certain difference significant. These tables are based on the fact that a relation appears to exist between the average coefficient of absorption and the corresponding standard deviation.[1]

For adults a normal C. A. is 95 % or more. This does not apply to young babies, however, as is shown in the following figure.

It appears that the younger a normal baby, the more likely is the C. A. to be about 85 %. An exception to this is the breast-fed baby, which always has a high C. A. *These values only apply when the diet contains sufficient fat.*

For instance, when butter milk is given to a child, who with ordinary milk has a C. A. of 95 %, values varying from 50—80 % are found! This is simply a consequence of the fact that the influence of the "endogenous" fat on the C. A. becomes greater when the quantity of fat taken up with the food is small.

[1] This investigation was carried out with the co-operation of the Statistics Department T. N. O., head Th. J. D. Erlee; cf. WEIJERS.

Determination of the fat absorption by examination of the blood

a) Measuring the lipaemia

On the basis of FRAZER's theory (cf. ELKES, FRAZER and STEWART) about fat absorption in the form of fat particles, it can be expected in the case of normal people that shortly after eating a meal, rich in fat, the quantity of fat in the blood greatly increases; the fat particles indeed enter the blood directly via the lymph system. Lipaemia can be ascertained by chemically determining the fat content of the blood. Because this method determines all fat ingredients in the blood, thus also those which are not directly derived from the dietary fat just ingested, FRAZER (cf. ELKES, FRAZER and STEWART) prefers to count the fat globules in the blood (the chylomicrons). In this way he obtains a real impression of the degree of the lipaemia. The chylomicrograph is useful as a means of obtaining information about a change in the distribution of fat during absorption.

However, the chylomicrograph and the chemical determinations of the fat content of blood are useless in the assessment of fat absorption, because it is clearly dependent upon rate of intake and output of fat into the blood as is already stated by FRAZER.

b) Vitamin A tolerance curve

Since the publication of MAY and MCCREARY (1941) regarding the relation between the severity of coeliac disease and the progression of vitamin A tolerance curve, new publications are continually appearing, especially in American literature, in which conclusions are drawn about fat absorption from the progression of the vitamin A tolerance curve.

The method is based on the assumption that the absorption of the fat-soluble vitamin A runs parallel with the absorption of fat.

Although the method is attractive for the clinic because the determination of vitamin A in blood can be carried out simply and accurately, the question is whether this parallelism really exists or not. As far as we know, this has never been examined with exactitude. Yet this is the first requirement, since on theoretical grounds, it is doubtful if a correlation would exist between fat absorption and the progression of the vitamin A tolerance curve, because the progression of this curve not only depends on the amount of vitamin A absorbed, but also on the manner and rapidity of absorption. On account of these objections we have compared the coefficient of fat absorption with the progression of the vitamin A tolerance curve in the case of some children. The results are summarized in fig. 7.

It is true that from the figure it appears that a rise of at least 10

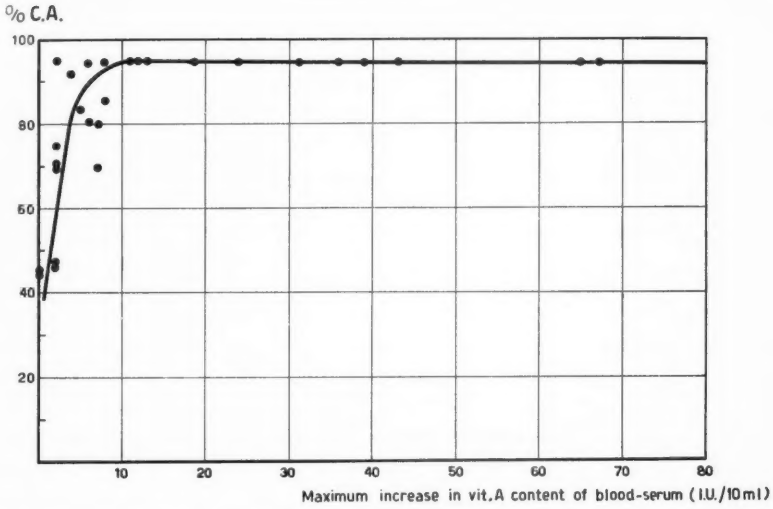

Fig. 7. Correlation of the coefficient of fat absorption with the maximal increase in the vitamin A content of the blood, after giving an oral test dose (10.000 I. U. vitamin A/kg of body weight) in coeliac disease.

units signifies a good fat absorption, for the rest no conclusions can be drawn from the progression of the curve as to the severity of the fat absorption defect. It can be expected that the quantity of vitamin A taken up before the

TABLE

Influence of the degree of saturation with vitamin A on the progression of the vitamin A tolerance curve in normal persons.

Date	Average C. A. in %	Progression of vitamin A tolerance curve expressed in I. U. vitamin A/10 ml serum			Dose of vitamin A in I. U.
		fasting	after 3½ hrs.	after 7 hrs.	
$^{13}/_{8}$ '49	95	3	4	5	10.000
$^{15}/_{8}$–$^{31}/_{8}$	daily 30.000 I. U. vitamin A in the form of Bluevita forte				
$^{31}/_{8}$ '49	95	3	37	22	10.000 per os
$^{31}/_{8}$–$^{21}/_{9}$	daily 30.000 I. U. vitamin A in the form of Bluevita forte also 100.000 I. U. vitamin A (Squibb forte 1 ml oil) intramuscularly				
$^{21}/_{9}$ '49	95	1	44	13	
	Another patient:				
	95	5	6	38	
	after giving extra vitamin A:				
	95	4	100	84	

vitamin A tolerance curve is determined will have an influence on the results, because it is very probable that a great influence is exercised on the progression of the vitamin A tolerance curve by the degree of saturation of the liver with vitamin A. This latter is dependent, not only on the absorption but also on the amount and form in which vitamin A is presented, and perhaps also on the liver function. This is clearly shown by the figures in the preceding table. Thus with uniform fat absorption the saturation with vitamin A can have a great influence on the progression of the vitamin A tolerance curve.

Summarizing, the conclusion is justified that a reliable impression of the fat absorption can only be obtained on the basis of the determination of the coefficient of absorption.

Fat excretion

In principle it is also possible that steatorrhoea is caused by *fat excretion* in the intestines. In spite of the work of VOIT, MÜLLER, HILL and BLOOR, SPERRY and BLOOR, SPERRY and ANGEVINE, and others, this possibility is hardly ever taken into account in practice. In the following articles we will try to explain that in coeliac disease steatorrhoea is wholly or partly caused by fat excretion. It is certainly not out of the question that in other diseases also, such as sprue, liver cirrhosis and others, steatorrhoea is caused by fat excretion!

The quantity of fat excreted in 24 hours is calculated by determining the amount of fat in the faeces. Daily determinations, calculation of the sliding mean and statistical evaluation of the results are necessary in this case, just as in calculating the coefficient of absorption. From the nature of things it is clear that no decision about fat excretion is reached by determination of lipaemia or of the vitamin A tolerance curve.

Summary

The value is discussed of various methods generally used in the assessment of disturbed fat absorption: microscopical and chemical determination of fat in faeces, expressed or not with regard to dry substance or calculated as coefficient of absorption, the measuring of a lipaemia or the determination of a vitamin A tolerance curve. Only the coefficient of absorption appears to be a good standard of measurement for the judging of disturbed fat absorption. To explain steatorrhoea besides an absorption disturbance, fat excretion in the intestines must also be taken into account.

Maladie coeliaque. I. Critique des différentes méthodes d'investigation.

On discute la valeur des différentes méthodes utilisées généralement pour évaluer les troubles de l'absorption des graisses, la détermination microscopique et chimique des graisses dans les faeces, exprimée ou non par rapport aux substances sèches, ou bien calculée comme coefficient d'absorption, la mesure de la lipémie ou la détermina-

tion de la courbe de tolérance à la vitamine A. Seul le coefficient d'absorption semble être un bon moyen de mesure pour juger les troubles d'absorption de la graisse. Pour expliquer la stéatorrhée, à coté des troubles d'absorption, l'excrétion des graisses dans l'intestin doit être aussi prise en compte.

Coeliakie. I. Kritische Wertung der verschiedenen Untersuchungsmethoden.

Der Wert der verschiedenen bei der Bestimmung der Fettabsorption benutzten Methoden wird diskutiert, die mikroskopische und chemische Fettbestimmung im Stuhl, zur Trockensubstanz in Beziehung gesetzt oder nicht, oder als Absorptionskoeffizient berechnet, das Messen einer Lipaemie und die Bestimmung der Vitamin A-Toleranzkurve. Lediglich der Absorptionskoeffizient scheint ein gutes Standardmass für gestörte Fettabsorption zu sein. Für die Erklärung der Steatorrhöe muss neben der Absorptionsstörung die Fettausscheidung in Darm ebenfalls in Rechnung gestellt werden.

Enfermedad celíaca. I. Crítica de los diversos métodos de investigación.

Se discute el valor de varios métodos empleados corrientemente en el estudio de los trastornos de absorción de las grasas, como son el exámen microscópico y químico de determinación de grasa en las heces, expresado o no en relación a substancia seca o calculado como coeficiente de absorción, la determinación de la lipemia o las curvas de tolerancia a la vitamina A. Parece que solamente el coeficiente de absorción es un método satisfactorio para poder juzgar sobre los trastornos de la absorción de las grasas. Para la explicación de la steatorrea junto a los trastornos de absorción la excreción de las grasas en los intestinos puede también ser tomado en consideración.

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Coeliac Disease

II. *The Presence in Wheat of a Factor Having a Deleterious Effect in Cases of Coeliac Disease*

by W. K. DICKE, H. A. WEIJERS and J. H. v. D. KAMER

A basic principle of current opinion on the dietary treatment of coeliac disease is that all starch-containing foodstuffs (with the exception of bananas) are injurious for the patient and must be avoided (HAAS, ANDERSEN, SHELDON, LOWE and others).

In contra-distinction to this view, we have learnt in the course of many years' experience in the treatment of cases of coeliac disease that it makes a great difference to the patient what kinds of starch-containing foodstuffs (cereals and starches) are included in the diet; in particular, whether or not wheat is used. If wheat is banished from the diet and rice flour, maize starch, peeled, boiled potatoes are given instead, the anorexia, vomiting and abdominal pain disappear, the acute attacks of diarrhoea cease, the faeces become darker in colour, the patient gains in weight and finally the growth in height becomes normal, or even more than normal. If wheat is given again, the anorexia returns, the attacks of diarrhoea reappear, the stools become more liquid and lighter in colour, the weight decreases and growth slows down or is arrested.

This clinical observation was confirmed by experimental investigation (DICKE and WEIJERS), by a method which has been described elsewhere (VAN DE KAMER, TEN BOKKEL HUININK and WEIJERS; WEIJERS and VAN DE KAMER).

For this purpose patients with coeliac disease were placed on a diet consisting of milk (standardized at $2\,^1/_2$ % of fat) or protein milk, eggs, lean meat, butter, margarine, vegetables, fruit juices, sugar, glucose and cereals and/or starches in measured amounts for each patient. Only the kinds of starch-containing foodstuffs were varied, but always in equivalent amounts with respect to starch content, while the other components of the diet remained unchanged. Sometimes a correction was made for the different protein contents of the various cereals and starches, by varying the amount of lean meat.

Mean Coefficient of Fat Absorption per Test Period, as Percentage: (All Periods were Consecutive, without Interruption)[1]						
Case and Test	Sex	Age (yrs)	Rice flour or maize starch + potato	Wheat flour	Rice flour or maize starch + potato	
A	M	15	87.6	71.4	85.5	
C^1	M	4		86.7	92.5	
C^2	M	4	94.9	81.3	94.3	
D^2	M	8		86.7	93.9	
E^1	M	5	95.1	84.8	93.9	
			Rice flour or maize starch + potato	Wheat flour	Wheat *starch*	
B	F	3	83.9	63.9	86.7	
D^1	M	8	95.4	74.9	94.1	
			Maize starch + potato	Rye flour	Maize starch + potato	
D^3	M	8	93.9	85.6	89	
			Maize starch + potato	Oats	Maize starch + potato	Oats
G	M	9	91.3[2]	85.3	95.5	89.6
			Maize starch + potato	Only 6 g maize starch no potato	Maize starch + potato	
E^2	M	5	91.8[2]	93.1	95.1	

[1] The percentages were calculated after having attained the new level.
[2] First period after admission to the hospital.

Every day or every second day the amount of faeces per 24 or 48 hrs was measured and the fat content of the wet stools was determined by the method of VAN DE KAMER, the fat excretion being calculated in grams per day. As the amount of fat ingested was known, the fat absorption coefficient could be calculated (WEIJERS and VAN DE KAMER).

Each diet period lasted 3—4 weeks; this is long enough to give the patient a chance to become adapted to the new diet, i.e. to reach a new level if necessary. This is usually attained after 10—14 days, but may take longer. Further, it is necessary to get sufficient data at the new level to permit a statistical analysis. The results are shown graphically (figs. 1, 2, 3 and 4) and in the table above. It should be noted that a descent of the absorption coeffi-

cient from 90 % to 80 % means a doubling of the number of grams of fat eliminated in 24 hrs.

Example of one of the tests: (D^1, D^2, D^3). An 8 year-old boy with coeliac disease: The test extended from 22nd Jan. 1949 to 10th Jan. 1950. The diet contained 68 g protein; approx. 50 g fat; approx. 245 g carbohydrate and approx. 1750 calories.

Period I. 22 Jan.—12 Feb.: Diet: 950 g milk ($2\,^1/_2$ % fat), 76 g glucose, 15 g sugar, 125 g carrots, 125 g apple purée, 150 g raw apple, 10 g butter, 10 g margarine, 1 egg, 100 g meat, 57 g maize starch and 250 g potato.

Period II. 12 Feb.—4 March. Diet: The 57 g maize starch were replaced by 57 g of rice flour; the meat was cut down to 80 g. The fat absorption coefficient over periods I and II was 95.4 % (faeces 56 g/24 hrs, fat content 4.6 %).

Period III. 4 March—23 March. Diet: The 57 g of rice flour were replaced by 65 g of wheat flour; the meat was reduced to 65 g.

Period IV. 23 March—13 April. The 250 g of potatoes were replaced by 55 g of wheat flour; the meat ration was increased to 85 g. Coefficient of fat absorption over periods III and IV was 74.9 % (faeces 121 g/24 hrs, fat content 10.3 %).

Period V. 13 April—30 May. The whole 120 g of wheat flour were replaced by 110 g of wheat *starch* (amylum tritici), the meat ration was raised to 120 g. The coefficient of fat absorption was 94.1 % (faeces 49 g/24 hrs, fat content 5.5 %).

Period VI. 30 May—22 June. The 110 g of wheat starch were replaced by 130 g of corn flour and the meat was cut down to 60 g. The fat absorption coefficient over periods V and VI was 94.2 % (faeces 57 g/24 hrs, fat content 4.6 %).

In order to ascertain that the patient had not undergone a spontaneous improvement but was still sensitive to wheat flour, a new wheat flour period was instituted.

Period VII. 22 June—28 Aug.: The 130 g corn flour were replaced by 130 g of wheat flour. The coefficient of fat absorption was 86.7 % (faeces 75.2 g/24 hrs, fat content 8.4 %).

Period VIII. 28 Aug.—11 Nov. Diet as in period I. Coefficient of fat absorption 93.9 % (faeces 57 g/24 hrs, fat content 5.3 %).

Period IX. 11 Nov.—9 Dec. The 57 g maize starch and 250 g potato were replaced by 130 g of rye flour. Coefficient of absorption 85.6 % (faeces 98 g/24 hrs, fat content 14.4 %).

Period X. 9 Dec.—10 Jan. Diet again as in periods I and VIII. Coefficient of absorption 89 % (faeces 88 g/24 hrs, fat content 5.9 %).

Upon statistical analysis of the coefficient of absorption it was found that the two wheat flour periods III + IV and VII showed significant differences from the preceding and succeeding periods without wheat flour. $P = < 0.001$.

The periods without wheat flour which were close together in time (I plus II and V plus VI, V being a period with wheat *starch*) showed no significant difference from each other. $P = 0.22$.

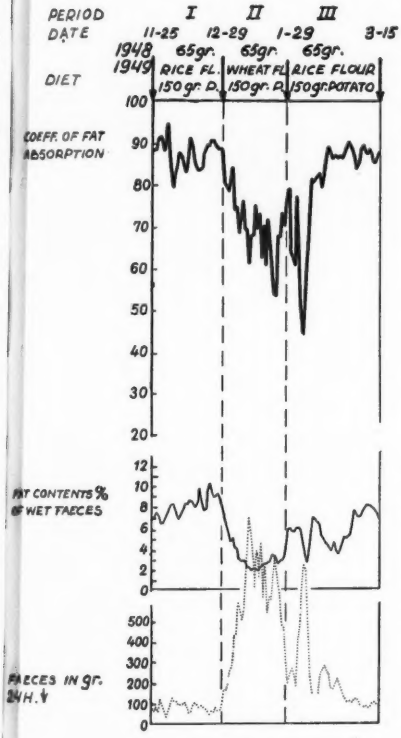

Fig. 1. Case A.

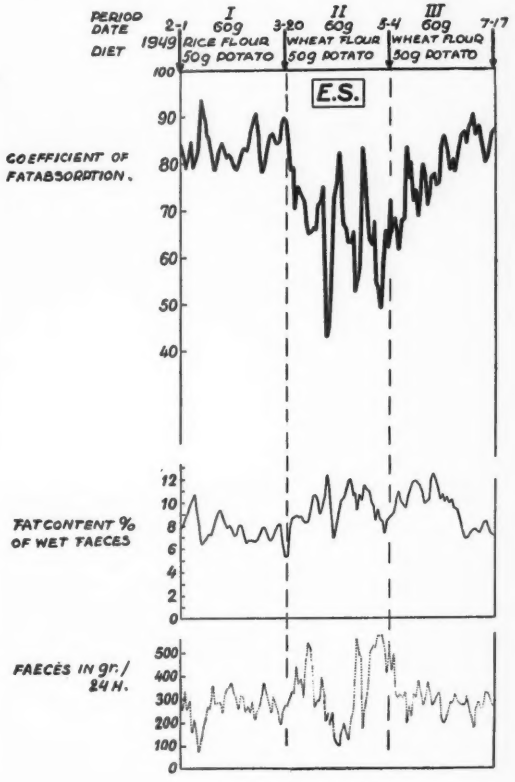

Fig. 2. Case B.

The two periods VIII and X without wheat flour are less satisfactorily comparable, because the recovery in X proceeded slowly, the period was short and the calculation was started immediately after the change of diet. In spite of this, period IX shows a significant difference from period VIII and period X. $P = < 0.001$ and $P = 0.032$. If we look at the periods IX and X on the graph we see a descending line in IX and an ascending line in X. Upon calculating the regression coefficients we find these to be of opposite sign and greater than $2 \times S_b$.

The wheat used was grown in the Netherlands; the flour was of 75 % extraction as provided at the experimental mill of the Cereals Department of the Institute for Research on Nutrition T. N. O. Analysis: protein 8.6 %; fat 1.3 %, carbohydrate 76 %; crude fibre 0.15 %. Free from baking additives and bleaching agents.

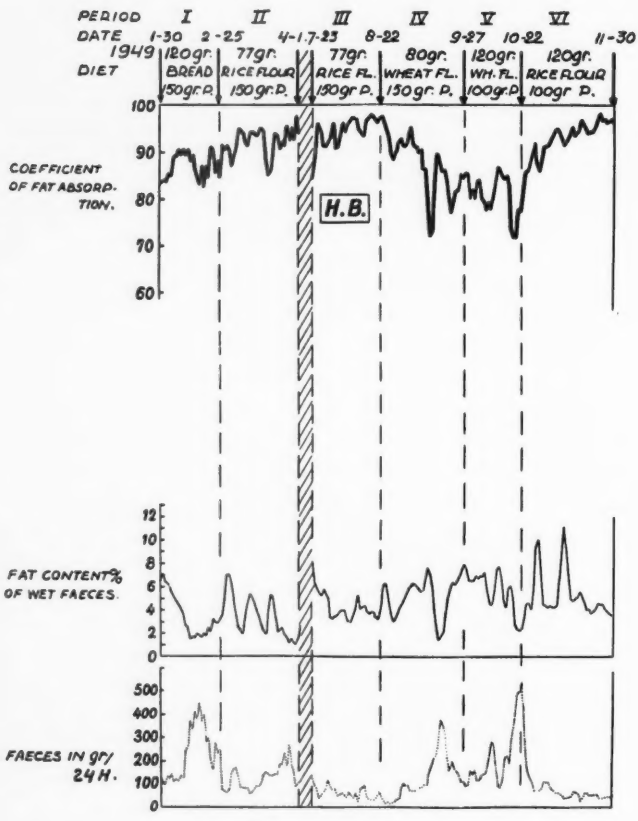

Fig. 3. Case C.

In addition to the data reported above, we are also in possession of the results of experiments with wheat flour on a fat free diet; these point in the same direction but will be published in another article.

Of the starch containing foodstuffs as far as investigated, the following are harmless; wheat starch, cornflour, maize starch, rice flour, and peeled, boiled potatoes.

Of the cereals and starches, wheat flour and rye flour and oats have a very unfavourable effect on the patient.

The other starch containing foods, such as barley, peas and beans, have not yet been tried and it is not known to which group they belong.

It was found, however, that no conclusions can be drawn as to the quantitative interrelations of the above-mentioned phenomena, since in one

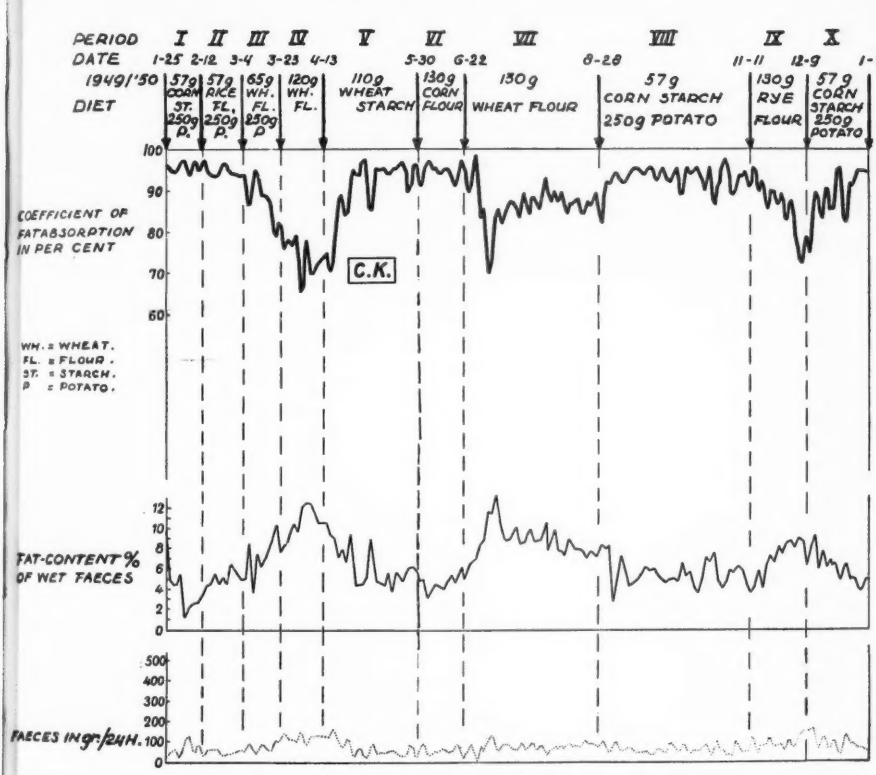

Fig. 4. Case D.

test period the increase in the volume of faeces may be the chief sign, while in another the fat content-percentage or perhaps the clinical signs may come more to the foreground. This is unpredictable. (See graphs 1—4.)

Discussion

A very remarkable and important fact is that while wheat flour shows the deleterious effect, wheat *starch* does not. Wheat starch is obtained by washing out kneaded wheat flour and allowing the starch to settle out of the washings, after which it is dried. Since the starch does not produce the harmful effect, one of the other components of the wheat flour must be responsible for this. Which component this is we do not yet know. For the time being we call it the "wheat factor."

The effect of rye and oats is supposed to be due to the same factor. We do not know whether the factor in question is also present in other starch containing foods.

As criteria for the diagnosis of coeliac disease we employed those which are in general use, as described, for instance, in the textbook of MITCHELL and NELSON. But even, should the reader make use of other criteria, this still does not in any way alter the wheat phenomenon as such.

It is also probable that this "wheat factor" is active over a wider field than in coeliac disease only. It is our clinical experience that some cases of dyspepsia and subacute enteritis in infants and young children respond very favourably to the wheatless diet. Exact laboratory proof is, however, not yet forthcoming.

However not all forms of steatorrhoea (e.g. fibrosis of the pancreas) are influenced by the "wheat factor." It still remains to be seen whether the difference in behaviour with respect to wheat will form a useful basis for a classification in which coeliac disease and related diseases can be brought together and also a clearer insight can be gained in the abortive forms.

It has by now become obvious that behind the alleged deleterious influence of carbohydrates on absorption there looms another still unknown harmful food constituent which exerts its damaging activities in the patient with coeliac disease either in the intestinal wall or deeper in the organism.

Conclusions

(1) A factor exists in wheat, which is the cause of anorexia, vomiting, diarrhoea and a large proportion of the fat elimination in patients with coeliac disease. However, this factor is not the wheat starch.

(2) Although anorexia, vomiting, diarrhoea and steatorrhoea are produced or exacerbated by the "wheat factor", there is no quantitative interrelation between these symptoms.

(3) The "wheat factor" has so far been encountered only in wheat, rye and oats.

(4) It is possible and perhaps even probable that this factor will also be found in certain other foodstuffs which have not yet been tested.

(5) It is probable that the "wheat factor" is active in other disturbances as well as coeliac disease (indigenous sprue, some forms of subacute dyspepsia and enteritis in infants and small children).

(6) The effect of the "wheat factor" may be of importance for the recognition and understanding of nutritional and intestinal disturbances.

(7) In investigations of improvements produced by medication or vitamins in cases of coeliac disease, the experimental set-up must take the "wheat factor" into account, in order to avoid wrong conclusions.

Summary

Attention is drawn to the different effects of different kinds of cereals and starches on patients with coeliac disease. The effect of wheat flour is unfavourable while that of wheat starch is harmless. The harmful effect is produced by a still unknown substance and not by starch. The substance in question is provisionally called the "wheat factor." The effect of this factor is judged according to its ability to produce or aggravate anorexia, vomiting, diarrhoea and steatorrhoea. Several conclusions as to the significance of this factor are presented.

Présence dans le blé d'un facteur ayant un effet nuisible dans les cas de maladie coeliaque.

On attire ici l'attention sur les différents effets des diverses sortes de céréales et d'amidon chez les malades atteints de maladie coeliaque. L'effet de la farine de blé est nuisible tandis que l'amidon de blé est inoffensif. Cet effet défavorable est produit par une substance encore inconnue et non par l'amidon. La substance en question est provisoirement appellée «facteur du blé». L'effet de ce facteur est jugé selon qu'il est capable de produire ou d'aggraver l'anorexie, les vomissements, la diarrhée et la stéatorrhée. Plusieurs conclusions sont présentées au sujet de la signification de ce facteur.

Ein im Weizen vorhandener, bei Coeliakie schädlicher Faktor.

Die Aufmerksamkeit wurde auf die verschiedenen Effekte verschiedener Arten von Getreide und Stärke auf Coeliakie-Patienten gelenkt. Der Einfluss von Weizenmehl ist ungünstig, während Weizenstärke harmlos ist. Dieser ungünstige Effekt wird durch eine bis jetzt nicht bekannte Substanz ausgelöst, und nicht durch Stärke. Diese Substanz wird vorläufig als „Weizenfaktor" bezeichnet. Die Wirkung dieses Faktors besteht in der Fähigkeit Anorexie, Erbrechen, Diarrhoe und Steatorrhoe zu verschlimmern. Einige Schlüsse über die Bedeutung des Faktors werden vorgetragen.

Presencia en el trigo de un factor mostrando efectos nocivos en casos de enfermedad celíaca.

Se llama la atención sobre los diversos efectos de diferentes clases de cereales y almidones en pacientes con enfermedad celíaca. El efecto de la harina de trigo es desfavorable, mientras que el almidón de trigo no es nocivo. Este efecto desfavorable es producido por una substancia todavía desconocida y no por el almidón. La substancia en cuestión es provisionalmente llamada «factor trigo». La acción de dicho factor se juzga de acuerdo con su capacidad para producir o agravar la anorexia, vómitos, diarrea y esteatorrea existentes. Se presentan varias conclusiones sobre la significación de dicho factor.

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Note during the correction: Our results have been confirmed by ANDERSON et al, SHELDON and LAWSON, and SÖDERHJELM:

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Bronchial Changes in Children with Primary Tuberculosis of the Lungs

by E. CARLENS and B. HELLSTRÖM

During the course of primary tuberculosis of the lungs in children chest radiograms often display fairly large, massive and initially homogeneous parenchymal densities. They usually extend over an entire lobe or segment. Their incidence varies in different age groups (25). The pathogenesis of such "epituberculosis" (6, 7) has been much discussed during recent decades. The discrepancy between the large radiographic changes and the benign clinical picture indicates that they are not due to an extensive tuberculous pneumonia, although tubercle bacilli have been demonstrated in punctate fluid from epituberculous infiltrations (24, 33). It has been suggested that the process might be an allergic one in which toxins from the tubercle bacilli produce an unspecific exudate around the tuberculous primary focus (3). But numerous necropsies have confirmed the hypothesis, which was advanced as early as 1926 (WALLGREN) that the observed pulmonary lesions often consisted of an absorption collapse following bronchial compression by the enlarged tuberculous glands (8, 30, 31, 36). These necropsy studies have also revealed the presence of glandular perforations into the lumen of the bronchus. Bronchoscopic investigations have afforded a means of observing the mechanism of this pathogenesis *in vivo;* and, particularly in recent years, a fair number of papers on this subject have been published (see Table 1).

The clinical symptoms and signs accompanying the bronchostenosis are: coughing, sometimes paroxysmal as in whooping cough and often having a metallic note, especially in infants, expiratory stridor, asthmatoid wheeze, and dyspnoea. These signs either occur in acute attacks or are present over longer periods. Cases are reported in which expectorated caseous masses have become impacted in the larynx and brought on attacks of suffocation, sometimes with a fatal outcome (1, 2, 20, 21, 27, 32). Many cases with extensive bronchial lesions have been devoid of clinical manifestations. The temperature shows individual variations; usually there is no fever. A high tempera-

TABLE 1

Bronchoscopic examinations in children with collapse or symptoms of bronchostenosis in primary tuberculosis of the lungs.

Authors	A No. of cases	B Positive findings	Per cent
MYERSON, 1940	29	8	28
JONES & coworkers, 1942	42	31	74
GÖRGÉNYI-GÖTTCHE & KASSAY, 1947	28	21	75
HUTCHISON, 1949	40	38	95
LEMOINE & coworkers, 1950	65	51	78
JEUNE & coworkers, 1951	50	50	100
LAFF & coworkers, 1951	15	7	47
HOWARD, 1951	59	44	74
ROGSTAD, 1952	41	38	93
ZUCCONI, 1951	50	22	44
CARLENS & HELLSTRÖM, 1952	23	18	78

ture suggests that there is an unspecific inflammation in the region distal to the obstruction or that the tuberculosis has spread by way of the bronchi. Such cases, therefore, are not solely atelectatic in nature.

When the collapse is extensive the physical signs are dullness and weak respiratory sounds but there are no rales. A prolonged expiratory phase and rhonchi are signs of bronchostenosis. Radiography is a great help in diagnosis. Bronchostenosis is often revealed by an ordinary examination, but the value of tomography has been reported (8, 28). The secondary changes in the lungs are demonstrated well on radiograms. In the majority of cases they consist of areas of collapse involving one or more lobes or parts of lobes. Often they exhibit a predilection for certain areas, the usual sites being the basal segments of the superior lobes or the apical of the inferior lobes. The collapsed areas are surrounded by compensatory emphysemas and when these are large they pull the mediastinum towards the same side. Sometimes the bronchostenosis functions as a valve instead. Then the result is an obstructive emphysema which pushes the mediastinum towards the contralateral side. To ascertain on what side the bronchostenosis is situated the movements of the mediastinum should be studied during respiration (Holzknecht-Jakobson's phenomenon).

By radiography alone, however, it is impossible to tell whether a bronchial compression is present with or without intrabronchial lesions. For such purposes bronchoscopy is the method of choice; it allows direct inspection of the lesions and offers the means of taking therapeutic measures. A number of such bronchoscopic studies from recent years are asssembled in Table 1. The

incidence of bronchoscopic changes varies in the series owing to the different indications for bronchoscopic examination, to the number of times it was repeated on the same patient, and to the different criteria for a positive bronchoscopic finding. It is convenient to distinguish two types of bronchial changes: extrabronchial and intrabronchial. The extrabronchial lesions observed by the authors listed in Table 1 were all compressions from outside the bronchus by an enlarged gland, resulting in various degrees of compression of the bronchial tube. Sometimes a caseous gland was seen gleaming faintly through the mucous membrane when perforation into the bronchus seemed imminent. The intrabronchial lesions consisted of congestion of the lumen with caseous necrotic masses extruding from the caseated tuberculous gland; inflammatory changes with hyperaemia and oedema in the mucous membrane; and as a common cause of bronchostenosis ridged granulations which at histological examination were found to be tuberculous. Many times the fistular opening was clearly seen, and large amounts of caseous material could sometimes be aspirated through it. Among other changes may be mentioned a widening of the carina when the glands at the bifurcation of the bronchi are involved, and when the glands in the external angle are enlarged there often is thickening of the spur-like process between the superior lobe bronchus and the bronchial trunk. Bronchial changes may of course be present even if the bronchoscopic examination is negative since there is nothing to prevent them from lying outside the range of the bronchoscope.

The type of anaesthesia constitutes a problem in bronchoscopic examinations. From a compilation by LAFF et al. (1951) it appears that only a few U. S. investigators have dealt with bronchoscopy during childhood. One reason for this may be that CH. JACKSON, the leading bronchoscopist, disapproves of the use of anaesthesia for bronchoscopy in children. In his latest handbook (1950) he stated: "No anesthetic, local or general, is necessary for bronchoscopy in children." Our and others' experience is that the patient should be so deeply anaesthetized that the bronchial branches to the suspected lung segment can be inspected at leisure without hindrance from reflex coughing. Coughing makes the bronchi contract spasmodically around the intubated bronchoscope. This gives rise to mucosal swelling, rubor and sometimes haemorrhages which make a true evaluation impossible. Moreover, anaesthesia reduces the risks of postbronchoscopic swelling of the glottis because the instrument is passed through a relaxed larynx. Trials have been made with a variety of anaesthetics. GÖRGÉNYI-GÖTTCHE and KASSAY used large doses of chloral hydrate which is a bit unsuitable if anaesthesia of short duration is desired. HUTCHISON tried penthotal-curare but thought that small children tolerated penthotal badly. He preferred and obtained good results with a nitrous oxide-trilene-curare combination. The majority of investigators have

TABLE 2

Site of collapse

	Right	Left
Superior lobe	6	6
Middle lobe	9	—
Inferior lobe	2	2

TABLE 3

Association between bronchoscopic findings and radiographic development of collapse

Bronchoscopic finding	Radiographic pattern 5 months after onset of collapse	
	No change or some regression	Normal or considerable regression
Normal (5 cases)	5	—
Compression only (5 cases)	5	—
Intrabronchial changes (13 cases)	7	6

reported good results with ether. Ether explosions are of course a theoretical danger but, as far as we know, no accidents have been reported. Chloroform will perhaps turn out to be a suitable anaesthetic; and according to WATERS (1951) chloroform anaesthesia should be reintroduced. This would seem to be particularly applicable in the case of bronchoscopy.

Test Subjects

The test series comprised 23 patients with primary tuberculosis in whom bronchostenosis was suspected.[1] Ages ranged from 10 months to 9 years and the children were anaesthetized with ether, after premedication with atropine. A course of penicillin was given for 2 days before and 3 days after bronchoscopy. The positions of the collapsed lobes are shown in Table 2; they were visible on all the patients' radiograms. These segmental or lobar collapses were situated on the right side more often than on the left. The middle lobe was affected particularly often (9 cases); in a few cases more than one lobe was involved. The findings made at bronchoscopy agreed with those of the other authors cited and are assembled in Table 3. In 18 instances bronchoscopic changes were observed at one or more examinations in the same patient. The lesions in 13 of these patients consisted of intrabronchial granulations or areas of caseous necrosis. All the patients were followed up with radiography at regular intervals for at least 6 months after the onset of collapse. The collapses on the whole remained stationary in those cases in which bronchoscopy disclosed normal conditions or the

[1] Altogether 85 cases of primary tuberculosis of the lungs were treated during the period covered by the bronchoscopic investigation.

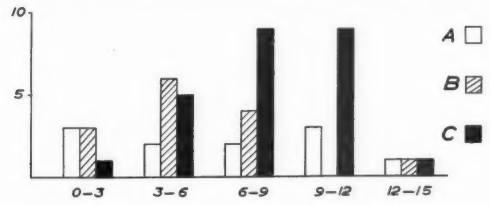


Fig. 1. Bronchoscopic findings and time relationship to the onset of primary tuberculosis. A = Normal finding. B = Compression only. C = Intrabronchial changes.

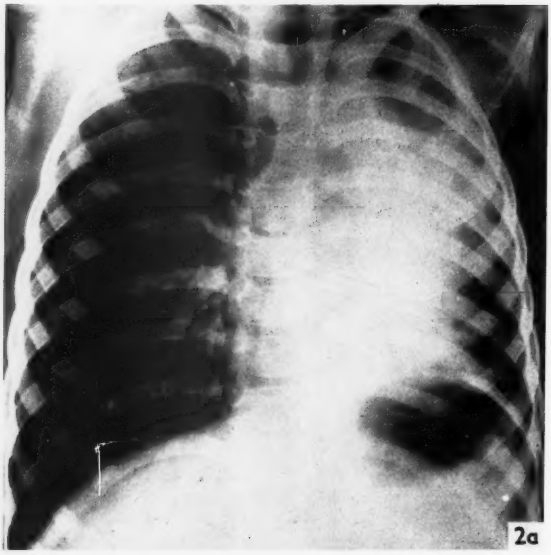
presence of an extrabronchial compression. When the intrabronchial changes were amenable to therapy the radiographic pattern was normal after 6 months or had on the whole regressed [in 6 cases].

The columns in Figure 1 represent different types of bronchoscopic findings in relation to the time which elapsed after the first observation of symptoms of primary tuberculosis. Bronchial compressions could as a rule be seen early; perforations or intrabronchial lesions did not usually appear during the initial 5 or 6 months (except one case after 2 months). The intrabronchial granulations although diminishing in size often persisted for as much as a year after the onset of primary tuberculosis. Only a few patients were examined bronchoscopically later than a year after showing tuberculous signs.

Limitations of space forbid full case histories, but a few typical cases will be reported below.

Comparatively late in the course of primary tuberculosis the left lung in the first case collapsed completely because of intrabronchial changes.

G. 8/50 (Fig. 2), *K. I.* This was a boy of 4 years who had not been BCG vaccinated. Initially he had fever on January 1st 1950. On admittance he was highly febrile and pale. The micro-E.S.R. was 35 mm, tubercle bacilli were found in the gastric lavage fluid, a chest radiogram disclosed left-sided hilar adenitis and small parenchymal densities on the left base. During the next few months there were no unusual developments. He soon became afebrile, the micro-E.S.R. remained fairly high, but a chest X-ray gave the impression that the tuberculous process had regressed slightly. The temperature rose once more in September, on the 16th of that month the chest *radiogram* showed collapse of the entire left lung. September 22nd, *bronchoscopy* revealed that the larynx and trachea were normal and the carina sharp. The right bronchial tree seemed normal. About half a centimetre below the carina the left main bronchus was completely filled with a greyish-white caseous material. When this had been removed the passage to the lung was restored. There was a slight oozing of blood from the bronchial wall which made it hard to tell where the caseous material came from. Afterwards the bronchoscope could be inserted deeper so that it was possible to inspect the bronchi of both the superior and inferior lobes. Their appearance was normal and the lung seemed well areated. *Biopsy:* The sections showed necrosis throughout and contained some calcifications. Each field of vision in the necrotic areas contained hundreds of tubercle bacilli. A *chest radiogram* taken on the same afternoon showed a partial clearing of the basal collapse. Five days later there was a considerable retrogression, and a month after that the radiographic pattern was practically normal. On October 26th



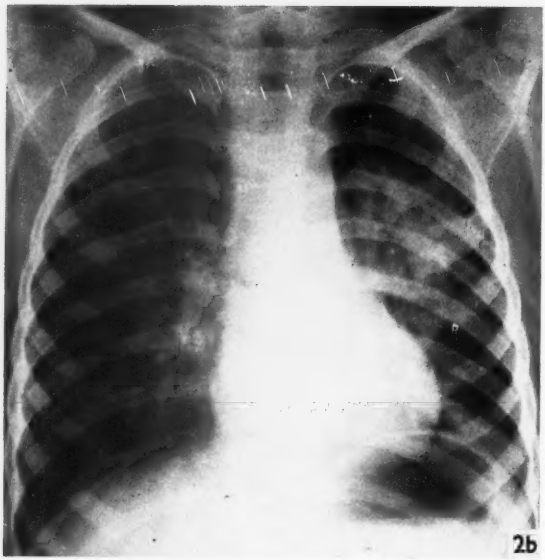
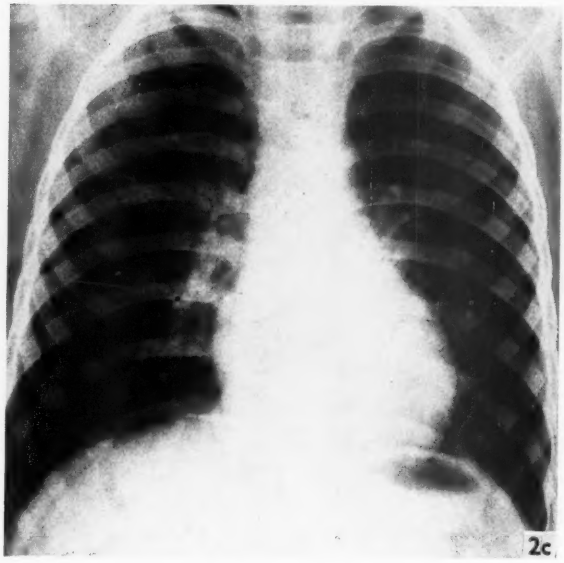


Fig. 2. Case 1. A. Radiographic appearance some hours after the first bronchoscopic examination with drainage, 22/9/50. The completely collapsed left lung is beginning to clear u basally. B. 5 days later: Most of the left lung is areated. C (see next page). A month later Normal radiographic appearance.

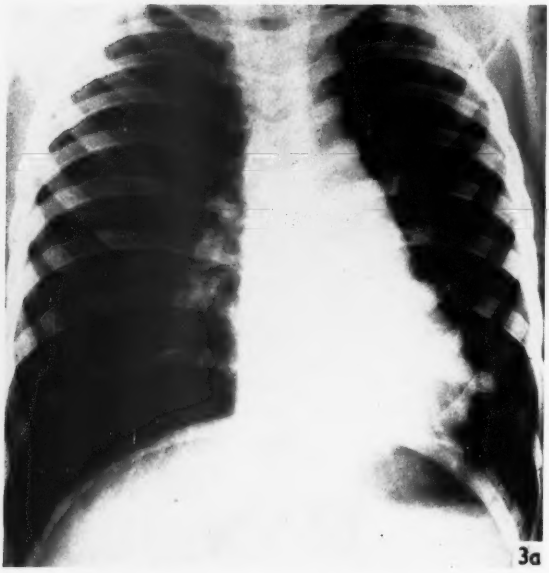


a renewed *bronchoscopic examination* disclosed normal conditions in the larynx, trachea and carina. The right bronchial tree looked normal. On the medial wall of the left main bronchus, about 1 centimetre below the carina there was a pea-sized lump of granulation tissue which occluded about half the bronchial tube. It was readily removed intact and the normal width of the tube was restored. The bronchial branches of the superior and inferior lobes were of normal appearance. A *chest radiogram* which was taken in September of the following year, i.e., 1951, displayed nothing abnormal.

* * *

Case 2 (Fig. 3) showed typical clinical signs of bronchostenosis. The radiographic signs were rather insignificant in this case, probably because exposures were made as early as 3 weeks before bronchoscopy.

G. 678/50, H. E. This was the case of a boy of 6 years who had not been BCG vaccinated. Initial fever October 15th 1950. Tired but not exhausted, he was admitted on October 23rd, when the micro-E.S.R. was 53 mm, the gastric lavage fluid was positive for tubercle bacilli, and hilar adenitis was observed radiographically on the left side. A refractory cough commences on January 1st 1951, which at first was thought to be bronchitic. Later he developed asthmatoid troubles with a wheezing respiration and physical signs in the form of rhonchi, initially over both lungs and in due course over the left base especially. A *chest radiogram* revealed an inconstant parenchymal density with diffuse borders at the base of the left lung, and also that the mediastinum was pulled slightly to the left. Because bronchostenosis was suspected *bronchoscopy* was done on May 9th 1951. It revealed nothing abnormal in the larynx and trachea. The carina was sharp and the right bronchial tree looked normal. The opening of the left main bronchus was filled to the brim with thick, red, lobulated masses of granulation tissue and the lumen appeared wholly occluded. These



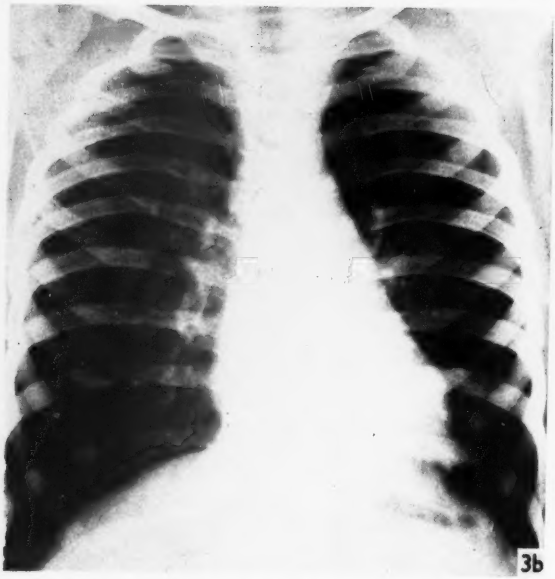
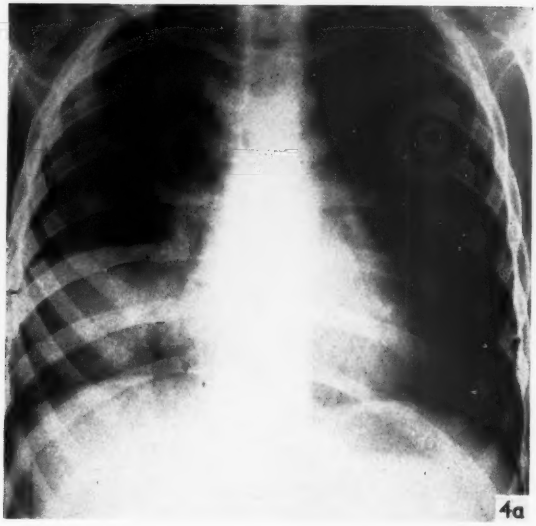


Fig. 3. Case 2. April 51. A. A small parenchymal focus is seen near the left contour of the heart in level with the first rib. There is a slight mediastinal displacement to the left with a compensatory emphysema at the right lung base. B. The day after bronchoscopic drainage of the left main bronchus the mediastinal displacement had diminished.



ig. 4. Case 3. Collapse of the middle lobe following bronchial occlusion. A. July 1950: Frontal iew. B. Side view. C. July 1951: Frontal view. The lateral segment still contains a probably fibrotic, indurated focus with small clear spaces (bronchiectasis?). D. Side view.

4c

4d

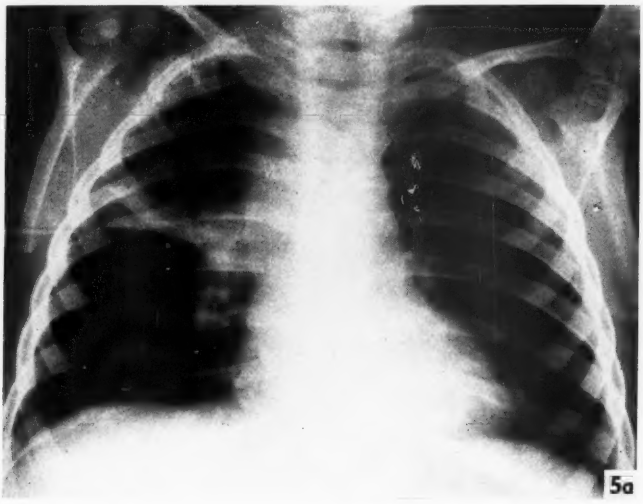


Fig. 5. Case 4. A. February '51. On the right there is a hilar enlargement and basally in the right superior lobe a parenchymal density. The bronchoscopic appearance was normal. B. September '51. The density in the right superior lobe has progressed. Bronchoscopy revealed a compression of the superior lobe bronchus and, a month later, caseous perforation. C. After bronchoscopic drainage the collapse underwent regression.

masses were excised with biopsy forceps. They contained not only mucous membrane but also fairly large amounts of a greyish-white, putty-like substance. Afterwards it was quite easy to pass the aspirator into the main bronchus whose width then seemed normal. Adrenaline was applied to all accessible areas with a brush. *Biopsy:* The extracted substance consisted of necrosed granulation tissue which contained rests of the bronchial wall, such as the cartilage ring, etc. Numerous fresh epithelioid cell tubercles with central necrosis, and Langerhans' giant cells were noted in the granulation tissue. *Diagnosis:* bronchial tuberculosis. At a *radiographic examination* the day after bronchoscopy the mediastinum was much less displaced and the signs of bronchostenosis were disappearing. Repeated *bronchoscopy* on January 11th showed that the larynx and trachea were normal. The orifice of the right main bronchus was completely normal. The orifice on the left side was still constricted to about half its normal size by granulation tissue and putty-like necroses, which chiefly came from the medial wall. When these protrusions had been snipped off the bronchoscope easily entered, revealing that below this region the bronchial tree was in no way abnormal. A gland probably had penetrated the medial wall into the orifice of the left main bronchus. *Repeated bronchoscopic check-up*, August 1st: The medial wall on the left side still exhibited a red and striated mucous membrane a few mm below the carina. No necrosed areas or caseous material was visible. The passage in the main bronchus seemed practically normal. The mucosal lesions were painted over a few times with a solution of adrenaline; and para-amino-salicylic acid and dihydrostreptomycin were given.

* * *

Case 3 (Fig. 4) is an example of collapse of the middle lobe following glandular penetration in a 6-year-old girl.

F. 387/50, B. B. The patient was a girl aged 6 who had not been BCG vaccinated and had initial fever in February 1950. She was then treated at another hospital for hilar adenitis on the right side. On June 18th she had a temperature, the *radiographic*

pattern was characterized by right-sided enlargement of the hilar glands, and by a parenchymal density extending throughout the middle lobe. On July 3rd she was admitted to the paediatric department, and was on arrival tired, rather pale and febrile. The respiratory sounds were weak and there was an area of dullness at the base of the right lung. *Bronchoscopy*, July 17th: The tracheal mucous membrane exhibited diffuse rubor; the carina was a bit on the broad side. A superficial inspection of the left bronchial trunk showed that it was of normal width and configuration. Just below the carina the medial wall on the right side was bulging inwards and occluding most of the lumen in the bronchial trunk so that the bronchi of the middle and inferior lobes could not be inspected. The mucous membrane over the bulge was hypertrophic, granular and bled easily. At the centre there was a greyish, necrosed region which exuded a small amount of purulent secretion. Together with a biopsy specimen from the granular region of the mucous membrane a lump of cheesy tissue measuring about 2 × 3 mm was obtained. The septum of the right superior lobe bronchus was thickened but its lumen was patent and of normal configuration. After only a few days the girl was afebrile, and then she rapidly recovered and put on weight so that in a month or thereabouts her general health was excellent. The radiographic appearance of the collapse remained more or less constant. At a *bronchoscopic examination* on August 22nd the larynx, trachea and carina were normal. The left side was not inspected. Immediately below the root of the right superior lobe the bronchial trunk was completely occluded by a greyish-white, gritty mass of granulation tissue. The latter was nipped with a pair of biopsy forceps and a clot the size of a baked-bean was removed intact. The downward passage became accessible readily and the bronchi of the middle and inferior lobes became visible. There was a small haemorrhage. At *biopsy* totally necrosed tissue rests were seen; direct samples of bronchial secretion contained tubercle bacilli. Following this bronchoscopic examination the parenchymal density began to clear up from the periphery inwards. Another *bronchoscopic* check-up on October 25th showed that there still remained a small rest of granulation tissue and it was removed. Radiography after this examination showed continued but not complete improvement. A node almost as large as a pea was observed on the medial wall at a further bronchoscopic examination on January 18th. It was snipped off. Slight additional regression was found *radiographically*, but a year after the onset of primary tuberculosis the lateral segment of the middle lobe still contained indurated areas with small translucent spaces (bronchiectasis?). The patient was subjected to therapy with para-amino-salicylic acid and dihydrostreptomycin.

* * *

Case 4 (Fig. 5) illustrates the importance of doing repeated bronchoscopies when the first one shows a normal picture. In this case the second disclosed bronchial compression and the third perforation.

F. 213/51, I. B. A 4-year-old girl had been BCG inoculated shortly after birth but not followed up. There was no vaccination scar. Initial fever set in on February 8th 1951. Radiography on February 14th revealed the existence of hilar adenitis on the right side and a massive, structureless density at the base of the superior lobe. Because the collapse persisted *bronchoscopy* was done on May 23rd. Larynx and trachea were normal and the carina sharp. The mucous membrane on the right side was pale. The entry to the superior lobe bronchus was of normal width. There were neither specific changes nor signs of stenosis to be seen. Tubercle bacilli were found in the

bronchial secretion by the guinea pig test. The girl's condition was followed up at the out-patient department. On September 5th she was readmitted for the persistent collapse. *Bronchoscopy*, September 10th: The larynx, trachea and carina were normal. The opening into the right bronchial trunk was normal. The superior lobe bronchus had its origin just below the carina and was slightly constricted. The mucous membrane was a bit red and bled easily. A delicate and flexible aspirator could be passed quite far into the superior lobe bronchus without obtaining much secretion or encountering stenosed areas. No perforation was seen. Now however, the *radiogram* revealed a shadow over the upper part of the right superior lobe. Repeated *bronchoscopy* on October 30th showed nothing abnormal in the larynx, trachea or carina. The right bronchial trunk seemed normal. This time the right superior lobe bronchus was seen to be completely filled with greyish-white caseous masses. They were removed easily with forceps; all told quite a lot was extracted. Afterwards the superior lobe was aspirated with a flexible aspirator, and this procedure removed abundant amounts. Towards the end of the examination it was observed that the superior lobe bronchus had an opening that was normally wide and patent. The superior lobe appeared to be well areated. *Radiographically* the collapse showed a distinct regression within a few weeks after the last bronchoscopic examination. The patient had para-amino-salicylic acid and dihydrostreptomycin therapy.

Discussion and Conclusions

The results of our investigations confirm previous findings, i.e. in most cases of so-called epituberculosis changes can be demonstrated in the bronchi, and the epituberculosis may itself be regarded as an absorption collapse secondary to such changes. ROGSTAD has proposed that the condition should be known by the term "*Lymphadenitis tuberculosa bronchostenotica.*" In order to study the nature of the bronchial changes it is necessary to use bronchoscopy. The question is, when is the procedure indicated, and has it a more than diagnostic value, and what risks does it involve?

When intrabronchial changes were present they were aspirated or removed as far as possible with forceps. Thereby the patency of the bronchial lumen was restored at least temporarily and the distal part of the lung was areated. Even if aspiration should remove only a small portion of the caseous masses such areation may create conditions in which any substances entering the bronchus can be expectorated. The radiographical equivalent of a better areation is the disappearance of the collapsed part of the lung. Half a year after the collapse regression was predominant or complete in 6 of the 13 patients with intrabronchial lesions. In the patients with normal bronchoscopic findings, in whom the lesions probably were situated farther peripherally, or in those in whom the only signs were constrictions of the lumens due to glandular compression, it was obviously impossible to better the areation. After half a year the collapse remained unchanged or showed only a slight regression. When collapse persisted for a considerable time fibrosis and in-

duration occurred in the collapsed parts of the lung — the region shrank more and more, and bronchiectasis frequently develops in shrinking fibrotic tissue. The incidence of bronchiectasis seems to be high; at bronchoscopic examinations in cases equivalent to ours the incidence of bronchiectasis reported in the literature ranges between 50 and 80 per cent (9, 13, 14, 16, 18, 26, 28, 35, 39). It is generally held that bronchiectasis is seldom accompanied by signs and symptoms (13, 26, 28, 37), but the period of observation was generally too short. In some cases the risk of such non-tuberculous sequelae is probably reduced by bronchoscopic drainage.

If the intrabronchial changes consist of large masses they may be caught, if expectorated, in the rima glottidis and give rise to a danger of suffocation. Such cases are rare but no curiosities. When glandular perforation is feared the risk of such accidents must be reduced by employing a fixed schedule of bronchoscopic examinations at intervals.

The association between glandular perforation and bronchogenous spread of the tuberculosis is a matter that needs unravelling. Bronchogenous dissemination might predispose to postprimary pulmonary tuberculosis (5, 34). The risk is generally considered small on the grounds that a caseous area contains proportionate, few tubercle bacilli. In one of our cases (No. 1), however, the aspirated material held hundreds of bacilli per microscopic field. This should mean that the risk of spreading is a real one, and it is doubtful whether it can be reduced by bronchoscopic aspiration of accessible regions.

When intrabronchial changes were present — sometimes with tuberculous granulations in the bronchial mucous membrane and a possible risk of spread — we thought it advisable to administer PAS (para-amino-salicylic acid) and streptomycin. Bronchoscopic examinations enables one among such patients to select those that would benefit by this therapy.

Bronchoscopy is not without its dangers during childhood; but we considered the risk negligible with the technique used. Complications as a result of this examination occurred in only one of our cases, with spontaneous pneumothorax and pleurisy which resolved rapidly. One must remember that more than 50 bronchoscopies were done altogether. To ensure that the examination could be completed and to reduce the risk of mucosal lesions with subsequent swelling, we considered it essential to have the child under general anaesthesia. The procedure can also be used in infants. In our series the youngest bronchoscoped patient was 9 months old.

We considered bronchoscopy indicated when lobar or segmental collapse persisted for more than 1—2 months. Spontaneous remission of the collapse is not seldom seen earlier than this in the course of primary tuberculosis. The causative factor in such cases is probably bronchial compression. In one of our cases the collapse involved the whole of one lung. Bronchoscopy should

in our opinion be done immediately when this occurs. One of the main bronchi is almost always perforated in cases showing plain signs of "pseudoasthma," and we feel that bronchoscopy should be done in these cases too. None of our patients had a typical obstructive emphysema, but in this condition bronchoscopy should be used to look for the cause of the valvular mechanism.

Summary

The authors examined bronchoscopically 23 cases of primary tuberculosis of the lungs in children with clinical or radiographic signs of bronchostenosis. Bronchial changes were observed in 18 cases. In 13 of these cases the changes were intrabronchial and associated with caseous necrosis and tuberculous granulations. The diagnostic and therapeutic rôle of bronchoscopy is emphasized.

Modifications bronchiales chez des enfants ayant une tuberculose primaire des poumons.

Les auteurs ont examinés bronchoscopiquement 23 cas de tuberculose primaire des poumons chez des enfants présentant des signes cliniques et radiologiques de bronchosténose. Ils ont observé des modifications bronchiales dans 18 cas. Dans 13 de ces cas les modifications étaient intrabronchiales et associées avec de la nécrose caseuse et de granulations tuberculeuses. Les auteurs mettent l'accent sur le role diagnostique et thérapeutique de la bronchoscopie.

Bronchialveränderungen bei Kindern mit Primärtuberkulose der Lungen.

Die Autoren untersuchten bronchoskopisch 23 Fälle von Primärtuberkulose der Lungen bei Kindern mit klinischen oder röntgenologischen Zeichen einer Bronchostenose. Bronchialveränderungen wurden in 18 Fällen festgestellt. In 13 dieser Fälle waren die Veränderungen intrabronchial und mit Verkäsung und tuberkulöser Granulation vergesellschaftet. Die diagnostische und therapeutische Rolle der Bronchoskopie wird hervorgehoben.

Alteraciones bronquiales en niños con tuberculosis pulmonar primaria.

Los autores han examinado desde el punto de vista broncoscópico 23 casos de tuberculosis pulmonar primaria que mostraban signos clínicos o radiológicos de estenosis bronquial. En 18 de ellos se encontraron alteraciones bronquiales. En 13 de estos casos las alteraciones eran intrabronquiales y asociadas con necrosis caseosa y granulaciones tuberculosas. Se destaca el valor diagnóstico y terapéutico de la broncoscopia.

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CASE REPORTS

Acute Blindness as Post-Measles Complication

by TORBJÖRN STRÖM

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Serious ocular complications with measles are uncommon. Many cases of lesions of the eye following this disease have, however, been reported, the majority perhaps due to secondary bacterial infection, but in other cases the lesion may be due to the effect of the measles virus on the visual organ with resulting optic atrophy or perhaps as a result of involvement of the visual pathway more centrally.

We have recently had a patient with an eye desease following measles, in which the course and the clinical findings differed from those most often manifested in this type of complication.

The patient was a six year old boy who had previously been in good health. On Aug. 16th, 1951, the patient developed a fever and a sore throat, while spending a holiday in the country. On Aug. 17th an eruption appeared and was diagnosed by a physician as measles. On Aug. 18th the patient vomited twice, his temperature was about 40° C and he was in a slightly dazed condition. The rash faded rapidly, and on Aug. 22nd he was rather languid but otherwise appeared to have recovered. The same evening a relative thought that the boy did not look as well as before. The next morning he was completely blind. He was brought to Stockholm and admitted to the Department of Ophthalmology at the Sabbatsberg Hospital on Aug. 25th.

Findings on admission Aug. 25th: General condition satisfactory. The patient played, and was afebrile. Right eye: uncertain perception. Left eye: perceived light. There was slight conjunctival congestion present in both bulbar conjunctiva. The pupils were dilated and did not react with certainty. The anterior parts were free of irritation bilaterally. The refractive media were clear. (No oedema was found in the cornea or lenses.) The disks were not clearly visible but did not appear to be choked. The veins were engorged, the arteries showed obvious narrowing. There was marked retinal oedema, nicking and small hemorrhages along the vessels. The pressure was normal. — S. R. 45 mm. White cells: 6,600 per c.mm. Cerebrospinal fluid: colourless, clear. Ten R. B. C.'s per ml, 1 W. B. C. per ml. Albumin: 26 mg per cent. X-rays of cranium, orbits and sinuses N. A. D. Transfer to Department of Paediatrics, Karolinska Sjukhuset.

Findings on admission to the Department of Paediatrics Aug. 26th: General condition not affected. The patient laughed, appeared euphoric and was cooperative during examination. He reacted adequately to pain and was fully conscious. He had no visual perception. — Pulse: 80, regular. Blood pressure: 115/75. Oral cavity, nose and pharynx: 0. Nose and throat tests showed a growth of normal flora. Lymph glands normal. Heart: N. A. D. Lungs: N. A. D. Abdomen: N. A. D. There was no

stiffness of the neck. Lasègue's and Kernig's signs: negative. Patellar, Achilles tendon, biceps, triceps and abdominal reflexes: normal. Babinski's reflex bilaterally: negative. Sensibility and muscular strength: normal. Eye examination: — Dilated pupils (atropine). Right eye: fine, moderate path of light. Congestion of vitreous body. The eyeground appeared indistinct, but the disk was paler and the vessels narrower than previously. Left eye: moderate path of light, otherwise similar to right eye. (Docent Huggert.)

Urine. Heller's, Almén's, Gerhardt's, and Legal's tests: negative. Microscopic examination: 2–3 R. B. C.'s, 3–4 W. B. C.'s, solitary casts per field. *Blood.* Hb: 13.5 g per cent. R. B. C. 4.7 million. W. B. C.'s 25,500 (rod 2 per cent, segm. 58 per cent, lymphoc. 40 per cent). E. S. R.: 36 mm. Antistreptolysin: 25 units per ml. Antistaphylolysin: 4.0 units per ml. Wassermann: negative. Paul-Bunnell test: negative. Toxoplasmin test: negative. Thymol reaction in serum: 3 units. *Lumbar puncture.* Clear fluid. Pressure 80 mm. Queckenstedt's reaction: positive. Pandy's and Nonne's tests: negative. Mastix test: no change. Cells: 5 W. B. C.'s, 0 R. B. C.'s per ml. Sugar: 15 mg per cent. (Blood-sugar 119 mg per cent.) *Electroencephalogram.* Dysrhythmia with ample slow frequencies.

Course. On Aug. 30th there was no distinct path of light. Moderate congestion of vitreous body. R. E.=L. E. The eyegrounds were approximately as before. The pupils were moderately dilated and did not react to light. — Sept. 5th: Possible reaction to light at commencement of examination, but later uncertain. Otherwise status quo. Sept. 18th: The media were now clear. In both eyegrounds, pale sharply defined disks were seen, and in the maculae small greyish-white foci of exudate. Pathologic papillomacular reflex. Entire retina was diffusely mottled. The lesions resembled most closely retinitis with secondary optic atrophy (similar to that described in the literature as retinitis stellata). The electroretinogram was extinguished. Oct. 2nd: The pupils reacted to light. The patient was able to localize strong light, but became quickly fatigued. Incipient paleness of both disks was found, and markedly constricted vessels. As a result of the severe retinitis, a progressive, secondary atrophy of the optic nerve occurred.

White blood cells: — Sept. 1st 25,100, Sept. 5th 13,100, Sept. 18th 6,300, Sept. 28th 5,500. On Aug. 31th urine test showed faintly positive Heller's test. Numerous red, 2–3 white blood cells and fairly numerous hyaline casts per field. The blood pressure was on the same day 110/70. Later the urine was normal by usual tests.

We had the impression in the Department that the patient's sight improved slowly from about Sept. 3rd, when for the first time he conclusively perceived strong light placed near his eyes. On Sept. 27th he was able somewhat hesitatingly to name single objects shown to him, e.g. a comb, pencil etc. From Oct. 5th until discharge his sight improved considerably. He could then distinguish fairly small objects, and could also state the colours of objects shown to him.

During the entire hospitalization the patient was afebrile. He was in continual good spirits, made no complaints and had no headache. Apart from amaurosis he appeared healthy. There were no demonstrable psychic changes. Electroencephalogram Sept. 24th: as previously, dysrhytmic with ample slow waves.

The patient was discharged on Oct. 12th.

After-examination at Department of Ophthalmology: — Oct. 15th: Visual acuity of right eye 5/50, left eye 5/20. The refractive media were clear. Eyegrounds: no change. — — — Nov. 12th: no change.

That the patient had really had measles we considered confirmed by the fact that

his mother, who had not previously had the disease, fell ill and developed typical measles on the day after the patient was admitted to the Department of Paediatrics.

In the literature I have only been able to find reports of four or five cases resembling the present one.

WEIGELIN reported a case of an eight year old girl who eight days after developing measles became entirely blind overnight. The ophthalmoscopic picture resembled the present one with the exception that the veins were constricted also. The cerebrospinal fluid showed a slight increase in pressure (180 mm water), no other sign of encephalitis was present. Two years later the patient had very weak sight in a small portion of the field of vision which had not been entirely destroyed.

PARKER HEATH described the case of a six year old boy who ten days after a moderate attack of measles, became blind in the course of one day. The condition of the eyes again resembled that in our case. The arteries "were reduced practically throughout the fundus to threads and apparently were carrying little, if any, blood. The veins were dark in colour and were reduced in calibre throughout, but relatively to the arteries were engorged." This patient was regularly examined several times a day: a certain variation was found in the calibre of the arteries, and on some days the patient perceived light very dimly. Ten days after becoming blind the patient suddenly stated that he could see, and his vision became gradually normal. During hospitalization the patient had typical symptoms of encephalitis and developed a serious psychic defect.

SCHLOSSBERG and PRIZER reported a similar case of a six year old boy who, four days after an exanthematous eruption of a mild form of measles, became blind overnight. On admittance to hospital the patient was in high spirits and very active. The ophthalmoscopic findings were as follows: — "The disk was somewhat hyperaemic, its outline blurred, particularly along the nasal margin, with about two dioptres of swelling present. The veins were moderately engorged, the arteries small, thread-like, with no evidence of thickening of the walls. There was no nicking at the arterio-venous crossings. Distributed throughout the fundus were numerous, small round hemorrhages. Other parts of the retinae were pale and oedematous. — Vision: No light perception." A couple of days later there was, as in our case dust-like obscuration in the vitreous body. The cerebrospinal fluid exhibited signs of encephalitis. Six months later this patient had a visual acuity of 4/200 in the right eye and 3/200 in the left.

A fourth case is described by STEWENS. A six and a half year old girl suffered a sudden loss of visual faculty five days after contracting measles. After eleven days she exhibited a typical picture of retinitis albuminurica bilaterally. No sign of renal affection was evident. The cerebrospinal fluid was normal, and there was no other sign of encephalitis. In the course of some weeks the disk again became rather redder, the vessels more engorged and the vision improved to 5/50.

SOTTOW described a case which is presumably referable to the same group as the others reported. He saw the patient, a nine year old girl, about two and a half months after she had contracted measles. She had lost the greater part of her vision about three weeks after the onset. After a short time her sight improved, only to deteriorate later. At the time of SOTTOW seeing the patient she exhibited "a characteristic picture of retinitis albuminurica in the third stage of the disease". No sign of renal involvement was found, but it was stated that she had had headache and vomitings in connection with the measles attack.

As no postmortem examinations of the eyes were made in these cases, any attempt to explain what had taken place can be only speculative. WEIGELIN considered that the only explanation could be embolism of the central retinal artery. PARKER HEATH discussed in detail the various possibilities and considered that "the site of the retinal lesion lay in the brain. The lesion probably consisted in a localized oedema or inflammatory process, perhaps associated with anomalous vascular arrangements." SCHLOSSBERG and PRIZER did not deal at length with the pathogenesis, but referred to some diagnoses made by various outstanding ophthalmologists who saw the patient. Among these diagnoses we have particularly noted 1) venous thrombosis with secondary changes due to altered blood supply, and 2) embolism of the central retinal artery.

In our case, as well as in several of the others reported, evidence was found of encephalitis. It would be natural to associate the loss of sight with this complication of measles ("localization" of measles). Transitory blindness is often observed during a lethargic stage of measles encephalitis, and a gradual loss of sight in connection with a distinct picture of optic atrophy has often been described. In the course and the ophthalmoscopic picture these cases have not borne resemblance to ours. At postmortem a number of changes in the brain are found following measles encephalitis which were summarized by LITVAK as follows: — 1) None found. 2) Congestion and petechial hemorrhages in the brain and spinal cord. 3) Thrombi of the small cerebral vessels. 4) Perivascular infiltration (not constant). 5) Perivascular demyelination (most constant). 6) Phagocytic glial cells with granules filling them. FERRARO and SCHEFFER (cit. NEAL) maintained that insufficient emphasis had been laid on the fact that numerous thrombi and lesions of the vessels are accompanied by oedema and hyperplasia of the endothelium. According to these authors, this may help to explain the pathogenetic peculiarities of the disease with its often bizarre and transitory nervous symptoms. FORD bases on a number of investigations his assumption that the pathologic process is more toxic and degenerative than inflammatory, a point on which opinion is divided (cf. among others APPELBAUM *et al.*).

The case of postmeasles blindness described by STEWENS is referred to by DUKE-ELDER as the example of what ophthalmologists call toxic exudative retinitis, pseudonephritic retinitis or retinitis stellata, a fundus picture completely resembling that found in the cases reported here. It is assumed to be due to a toxic destruction of the capillary endothelium and is observed in a number of affections such as measles (STEWENS), influenza, erysipelas etc., and in a number of diseases of purely vascular circulatory nature, and has on several occasions been reported as suddenly attacking apparently completely healthy individuals.

If we compare the pronounced vascular lesions of measles encephalitis with the ophthalmoscopic picture which is also characterized by lesions of the vessels, we may well imagine that our patient had had measles encephalitis which had attacked the eyes as a phylogenetic part of the brain. Measles encephalitis often exhibits symptoms of a mainly localized lesion of the brain. On account of the blood supply peculiar to the eye, lesions of the vessels, accompanied by the failure of or greatly reduced blood supply, may rapidly lead to the dramatic disease picture we observed in our patient.

Summary

A six year old boy, six days after the outbreak of measles exanthema and an otherwise normal course of measles, became blind overnight. On admittance to hospital

he was amaurotic, otherwise afebrile and subjectively in good health. The cerebrospinal fluid and electroencephalograms provided evidence of encephalitis. Examination of the eyes showed fundal lesions dominated by markedly reduced arteries, pronounced retinal oedema and small hemorrhages. Five similar cases are briefly reported from the literature. Compared with the pronounced vascular lesions of the brain found in measles encephalitis, it is assumed that the disease picture may be attributed to encephalitis localized to the eyes as a phylogenetic part of the brain.

Cécité aigüe, comme complication de la rougeole.

Un garçon de six ans devint aveugle en une nuit, six jours après l'apparition de l'exanthème d'une rougeole, dont le cours était normal par ailleurs. A son entrée à l'hôpital, il était amaurotique, mais d'autre part afébril, et subjectivement dans un état normal. Le liquide céphalo-rachidien et l'électroencéphalogramme prouvaient la présence incontestable d'une encéphalite. L'examen du fond d'œil montrait des lésions dominées par une réduction marquée des artères, un œdème prononcé de la rétine, et de petites hémorragies. Cinq cas similaires sont brièvement rapportés dans la littérature. Par comparaison avec les lésions vasculaires prononcées du cerveau dans l'encéphalite de la rougeole, on présume que ce tableau clinique peut être attribué à une encéphalite localisée aux yeux comme une part phylogénétique du cerveau.

Akute Blindheit als Komplikation nach Masern.

Ein 6 Jahre alter Knabe wurde, 6 Tage nach Ausbruch des Masernexanthems und bei normalem Krankheitsablauf, über Nacht blind. Bei der Krankenhausaufnahme war er amaurotisch, sonst in gutem Gesundheitszustand und afebril. Der Liquor cerebrospinalis und das Elektroencephalogramm ergaben Zeichen einer Encephalitis. Bei der Untersuchung des Augenhintergrundes beeindruckte das deutliche Zurücktreten der Arterien, daneben Retinaödeme und kleine Blutungen. Fünf ähnliche Fälle sind kurz aus der Literatur erwähnt. Im Hinblick auf die ausgesprochen vaskulären Veränderungen des Gehirnes bei Masernencephalitis wird angenommen, dass dieses Krankheitsbild einer Encephalitis im Bereich der Augen als eine phylogenetische Partie des Gehirns zugeschrieben werden kann.

Cuguera aguda como complicación post-sarampionosa.

Un niño de 6 años de edad seis días después de la desaparición del exantema sarampionoso que por otra parte había tenido un curso normal se quedo ciego durante la noche. Al entrar en el hospital tenía amaurosis, estaba afebril y subjetivamente se encontraba bien. El examen del líquido cefaloraquideo y la exploración electroencefalográfica mostraban la existencia de una encefalitis. El examen ocular mostraba lesiones del fondo de ojo consistentes en reducción marcada del calibre arterial, pronunciado edema de retina y pequeñas hemorragias. Cinco casos similares son comentados brevemente de la literatura. Comparado con las pronunciadas lesiones vasculares cerebrales que se encuentran en la encefalitis sarampionosa, es presumible que este cuadro clínico pueda ser atribuido a una encefalitis en la parte del cerebro que es localizado a los ojos.

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Stenosis of the Larynx in Infancy

Haemangioma of the Larynx

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In infancy the larynx presents several special anatomical and physiological features which greatly predispose to the development of stenosis. As well as occupying a higher level than that of the adult larynx, the infant's larynx (at the level of the third and fourth cervical vertebrae) is of very small dimensions. The rima glottidis measures only about 7 mm in the sagittal plane and about 4 mm at its widest. The aditus laryngis is also small, and the epiglottis is directed more backwards than in adults. The cartilage of the larynx is soft and pliable, and the mucous membrane is comparatively thick and richly endowed with glands producing mucus. Over the anterior surface of the epiglottis the mucous membrane is loose and lightly attached, whereas it is securely attached along the free border and over the posterior surface of this structure. Oedema in this region tends therefore to press the epiglottis backwards and to diminish the opening still further. However, oedematous fluid in this region can escape easily into the hypopharyngeal tissues, although this is not possible in the region of the subglottis because of the ring of cartilage. With the onset of stenosis there is irritation of the mucous membrane leading to an increased secretion of mucus, the respiration rate increases and the passage of air through the larynx becomes still more difficult.

The most common cause of stenosis of the larynx in infancy is inflammation in or about it, — laryngitis, laryngo-tracheo-bronchitis and retropharyngeal abscess. Foreign bodies and the irritation they set up may also be to blame as well as congenital malformations in or about the larynx, — cervical cysts, mediastinal tumours, atresia of the oesophagus, micrognathia, macroglossia, hamartoma and, in the larynx itself, flattening of this structure, cysts and other tumours.

Though tumours of the larynx are rare in infancy, this possibility must be borne in mind when there are signs suggestive of stenosis. The most common tumours are cysts and polypi. Haemangiomas are sometimes found.

Fig. 1. The arrow points to the tumour in the larynx.

In 1944, *Ferguson* collected ten cases of haemangioma of the larynx in infancy published in different parts of the world and added a case, which he had himself observed. In the literature at my disposal I have not succeeded in finding any further publications on this subject. Recently we have observed the following case:

The patient was a female infant born three weeks before term. Birth was spontaneous and without complications, weight on birth 2900 g, length 48 cm. She was asphyxiated at birth and it was about 15 minutes before breathing became normal. She continued to be listless for the first 14 days. She did not take well at the breast, and the mother noticed that something was wrong with her respiration, inspiration in particular being laboured. When she was about 2 1/2 months old, she had to be admitted to hospital because of difficulty in respiration with attacks of cyanosis. At this stage she was very ill, but she rallied after treatment with steam and penicillin. She was discharged after five days, but within a few days her symptoms recurred and she was admitted to the University Pediatric Hospital in Bergen at the age of 3 months.

On admission her state of nutrition was good and she cried vigorously but rather hoarsely. Temperature 37°.4, pulse 132, regular and strong, respiration 30. There was slight inspiratory stridor, but no play of the alae nasi or inspiratory retractions. Mucous membranes clean, tonsils of normal size and without tonsillar plugs or deposits. Throat normal. Scanty sounds of bronchitis over the lungs. Otherwise no sign of disease on clinical examination.

Soon after her admission to hospital her respiration became more laboured and there was a definite inspiratory stridor with a dry, barking cough. Her discomfort

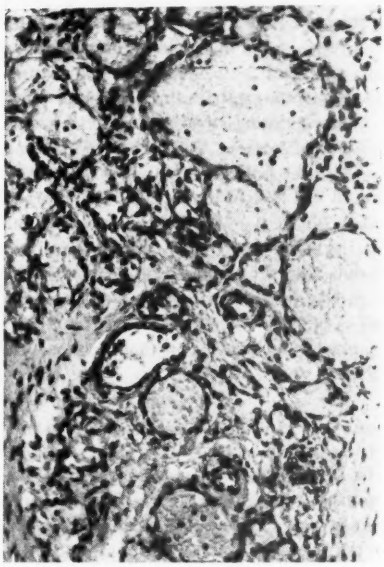

Fig. 2. Large cavities in the tumour filled with blood, in some parts small capillaries. (× 160).

increased in spite of steam, ephedrine and penicillin. Her temperature was normal but there was play of the alae nasi and considerable inspiratory retractions were observed. She improved after a few days. A radiological examination showed nothing abnormal with the larynx, trachea, lungs, oesophagus, stomach or duodenum. Electrocardiogram was normal and nothing pathological was found in the urine or blood. A direct laryngoscopic examination by a specialist showed there was a bulge in from the left in the wall in the region of the subglottis. It looked as if the mucous membrane was pressed in at this point. Bronchoscopy showed diffuse injection of the mucous membrane of the trachea and bronchi with an accumulation of tenacious mucoid exudate.

Directly after this examination her symptoms became more marked. Her condition quickly became very alarming with progressive general cyanosis, listlessness and collapse. Low tracheotomy was performed and some mucus aspirated. She rallied at once, and the cyanosis disappeared. But soon afterwards the attacks of cyanosis recurred and she died 45 minutes after the tracheotomy, four days after admission to hospital.

A post-mortem examination was carried out about 45 minutes after death. There was nothing noteworthy about the outer or inner tracheotomy opening situated at the level of the 5—6 cartilage ring. In the larynx, just distal to the left vocal cord, a dark blue, soft tumour, of the size of half a bean, was found in the mucous membrane (Fig. 1). It was flat and tapered off quickly to the periphery, merging diffusely with the mucous membrane which was oedematous, swollen and injected. There was much mucus in the trachea whose lining was plainly injected. In the main bronchi also the

mucous membrane was injected and plastered with mucus. The surfaces of the lungs were glistening, and there were small subpleural haemorrhages. There was atelectasis of both lungs which were practically air-less, sinking in water. The post-mortem examination showed no other pathological findings of special interest, and it was noted in particular that no haemangiomas were found elsewhere.

A microscopic examination of sections from the tumour of the larynx (Fig. 2) showed heaps of tumour tissue cells in the mucous membrane. These cells were regular in shape, flat to cubic, forming small capillaries and slightly larger hollow spaces filled for the most part by erythrocytes. There were several recent haemorrhages into the tumour tissue. No cell-atypia or infiltrating growth. Over a small area corresponding to the point at which the tumour bulged into the lumen of the larynx there was a lack of epithelium. Sections from the lungs showed marked atelectasis and hyperaemia but there were no collections of cells in the alveoli. Near the pleura there were small haemorrhages. There was some mucus in the bronchi whose walls in a few cases were thickened and oedematous.

Discussion

Sweetser has described two clinical types of haemangioma of the larynx, one in adults and the other exclusively in infants. The latter type is very rare, and here the tumour is situated in the region of the subglottis, being flat, diffuse, soft and bluish-black. This infantile type is congenital. Haemangiomas are regarded as benign tumours, but sometimes they may become malignant and give rise to metastases.

The disease is equally common in the two sexes, and in infancy always situated in the region of the subglottis. This is why symptoms of stenosis appear very early and are of the inspiratory type. They may exist at birth or come on directly afterwards. It is characteristic of haemangiomas of the larynx that the symptoms of stenosis vary greatly from time to time, being dependent partly on the degree of congestion of the tumour with blood, partly on the oedema of the mucous membrane and the secretion of mucus.

The objective findings bear no relation whatever to the patient's distress, and he shows no sign of toxaemia, Yet such patients are very liable to suffer from complications such as bronchitis and pneumonia.

In the histories of all the cases hitherto published reference is made to dyspnoea varying in degree and occurring in bouts with characteristic remissions. The attacks are said to recur again and again with symptoms becoming constantly more alarming. They often begin immediately after birth. Haemangiomas elsewhere in the body also suggest that the larynx tumour may be a haemangioma, but it should be borne in mind that haemangiomas of the skin are common in infancy.

Other clues to the diagnosis may be found in a radiological examination of the larynx. Indirect laryngoscopy is impossible in infancy, and we must therefore depend on direct laryngoscopy. It is, however, very difficult to obtain a clear picture of the subglottis region, and in most cases all that can be seen is only a bluish-black swelling. This should be enough to make us diagnose or, at least, suspect a haemangioma. The diagnosis can be confirmed by a histological examination, but biopsies in this region are dangerous because of the great risk of haemorrhage.

When stenosis of the larynx is acute, an immediate tracheotomy is often life-saving. As any stenosis of the larynx may be due to a haemangioma, a low tracheotomy should be chosen in order to avoid haemorrhages serious enough to threaten life.

There are several reasons why tracheotomy should be performed when there are grounds for suspecting a haemangioma. The relief afforded by this operation will reduce the size of the tumour. Besides, these patients are liable at any moment to develop more serious symptoms threatening life. Further, after the completion of tracheotomy it is possible to examine the patient with greater ease and security than before. Patients who have suffered from air-hunger for a considerable time are relatively less resistant to an extra strain and are apt to develop complications in the form of bronchitis and pneumonia.

With regard to more active treatment, mention should be made of radiotherapy, radium in particular being recommended. It is also well to note that such treatment may be followed by a transitory exacerbation of the symptoms, and a preliminary tracheotomy should therefore be performed. When no other treatment is effective, the operative removal of the tumour may have to be considered.

Hitherto the prognosis has been bad chiefly because of the difficulties in diagnosing this condition. An early diagnosis, early tracheotomy and X-ray or radium treatment would assuredly improve the prognosis.

In our case it is possible that the disease would have run another course had tracheotomy been performed earlier. This would have cured the patient's oxygen-hunger and have enabled us to carry out laryngoscopy and bronchoscopy under better conditions and with greater safety. Had this procedure been followed immediately by treatment with radium, it is conceivable that the tumour might have been removed.

Summary

A 3-months-old girl suffered from difficulty in inspiration from birth. Attacks of dyspnoea set in gradually with stridor, cyanosis and loss of consciousness. There were repeated remissions. Direct laryngoscopy revealed a bluish-black swelling in the region of the subglottis, and a post-mortem examination showed a haemangioma in the larynx with haemorrhage, tracheo-bronchitis and atelectasis of the lungs. In connexion with this case a brief account is given of the symptomatology, diagnostic possibilities and treatment of haemangioma in the larynx.

Sténose du larynx chez le nourrisson. Hémangiome laryngé.

Une fillette de 3 mois souffre de difficultés inspiratoires depuis la naissance. Des attaques de dyspnée commencent progressivement avec stridor, cyanose et perte de conscience. Il y eut des rémissions répétées. La laryngoscopie directe met en évidence une tuméfaction noir-bleuâtre dans la région sous-glottique, et l'examen post-mortem montra un hémangiome laryngé avec hémorragie, trachéo-bronchite et atélectasie des poumons. En relation avec ce cas, on rappelle brièvement la symptomatologie, les possibilités diagnostiques et le traitement de l'hémangiome du larynx.

Larynxstenose im Kindesalter. Hämangiom des Larynx.

Ein 3 Monate altes Mädchen leidet von Geburt ab an erschwerter Inspiration. Anfälle von Dyspnoe wechseln ab mit Stridor, Cyanose und Bewusstseinsverlust. Wiederholte Remissionen traten ein. Die direkte Laryngoskopie ergab eine bläulichschwarze Schwellung in der Subglottisgegend und die postmortale Untersuchung erbrachte ein Hämangiom des Larynx mit Blutungen, eine Tracheobronchitis und Atelektase der Lungen. In Zusammenhang mit diesem Fall wird ein ausführlicher

Bericht über die Symptomatologie, die diagnostischen Möglichkeiten und die Behandlung der Larynxhämangiome gegeben.

Estenosis de la laringe en la infancia. Hemangioma de la laringe.

Se trata de una niña de 3 meses de edad que desde el nacimiento tiene dificultad inspiratoria. Presenta accesos disneicos que aumentan gradualmente acompañados de estridor, cianosis y perdida de conocimiento. Se presentan repetidas remisiones. La laringoscopia directa muestra un abultamiento azul-obscuro en la region subglotica y en la necropsia se encontró un hemangioma de la laringe con hemorragias, traqueobronquitis y atelectasia pulmonar. En relación con este caso se hace una breve descripción de la sintomatología, posibilidades diagnósticas y tratamientos de los hemangiomas de la laringe.

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Acute Diffuse Infantile Sclerosis of the Brain (Krabbe's Disease)

(A report on Two Cases in Sibs)

by ARNE KÅSS

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The degenerative processes in the central nervous system constitute a series of heterogeneous conditions which together form a comprehensive chapter in which there is no satisfactory classification, and aetiology and pathogenesis are obscure. These processes are heredo-familial and, in spite of variations in their manifestations, they show some features in common (1). Contrary to the subjects with congenital defects, the persons who suffer from these diseases are normal at birth. The onset of the initial symptoms being very insidious, it is usually impossible to say exactly when the disease started. It often runs a very slow, uniformly progressive course. The hereditary transmission of the disease is recessive, but the reason why the familial char-

acter of the disease sometimes is not recognized might be due to lack of information or aberations from the typical Mendelian pattern. These degenerative processes tend to make their appearance at the same age among brothers and sisters and cousins, but the time at which they occur may vary in different generations. The symptomatology, the time at which the disease makes its appearance, and certain other factors may vary in different families with the result that identical clinical pictures are rare. There are also transitional and abortive forms differing from the classical picture.

Sir WILLIAM GOWERS applied the term abiotrophy to the heredofamilial, degenerative processes with their primary seat in the nervous system. Certain familial, degenerative diseases of the nervous system seem to depend on an inherited predisposition to disturbances of metabolism. Their pathogenesis is often obscure, and the conception of abiotrophy has been widened (2) so as to include all the heredo-familial, progressive diseases of the neuro-muscular system. They may include symmetrically distributed tissue necrosis with diseases of the nervous system and hereditary myopathies etc.

The cerebral degenerative processes are difficult to classify, and in addition to the degenerative lesions mainly concerned with the lenticular nuclei and abiotrophies with selective degeneration of special parts of the central nervous system, we may recognize three main groups (3):

(1) Lipoid cell degenerations including the Tay-Sachs disease and other lipoidoses in which the nervous symptoms are not usually the main feature. — (2) Degenerative conditions in which the grey matter in particular is the first structure to be involved. Records of such cases are rare, and various terms have been applied to them, distinctions being made between infantile and juvenile types. — (3) Degenerations of the white matter of the brain, Leucodystrophia cerebri or cerebral sclerosis is the largest and most thoroughly investigated group.

Common to all types (4) of familial cerebral sclerosis are the initial mental and motor disturbances. The child becomes stamped, according to his age, by a striking sluggishness and incapacity to take interest in his surroundings, or he is irritable or shy, or presents some other psychic change which in every case is the forerunner of a gradual development of complete dementia. Pareses set in insidiously parallel with the psychic disturbances, and when the patient is an infant his activities are much reduced, and when he is older the disease may make its first appearance with disturbances of gait. The pareses are accompanied by growing muscular rigidity which may end in flexor or extensor contractures and the like, merging into complete decerebrated rigidity. There may be a state of hyperirritability suggestive of tetany, tremor, athetosis or muscular twitchings as well as regular epileptiform convulsions. The tendon reflexes are often increased, but may be normal, and sometimes it may be impossible to evoke them, partly because of increased tone. Nystagmus and changes in the pupils may be observed, but disturbances of vision in the early stages of the disease are more rare in children than in adults. The ophthalmoscopy may show a normal fundus or changes in the optic disc indicative of neuritis or atrophy of the optic nerve. Apart from these findings a cerebral blindness often develops in the later stages of the disease, being frequently accompanied or preceded by a cerebral deafness. In the later stages of the disease irregular periods of fever, to some extent high, are apt to occur, and the disease ends with death (often with the picture of progressive cachexia) after five to six months or up to as many years according to the different types.

The heredo-familial sclerosis of the brain in childhood is classified thus:

(1) A chronic form, — Pelizaeus-Merzbacher's disease.
(2) A subacute form, — Scholz's disease.
(3) An acute, infantile form, — Krabbe's disease.

The chronic form of sclerosis of the brain, the PELIZAEUS-MERZBACHER disease, begins early in childhood, at the age of 1 to 5 years, with ocular symptoms, spasticity, ataxia, disturbances of speech and tremor, the picture presented being that of multiple sclerosis to which Parkinson-like conditions may be added later on. The disease progresses rather rapidly during the first years, with increasing dementia. Later on it may be quite stationary for several years, and the patients may reach adult life.

SCHOLZ's subacute juvenile type develops slowly from the age of 7—8 years with initial psychic and motor disturbances which gradually pass over to decerebrated rigidity during which there are frequent attacks of convulsions. As a rule the patient dies a couple of years after the first appearance of clinical symptoms.

KRABBE's acute infantile type of diffuse sclerosis of the brain was described in 1916 as a disease sui generis. The disease attacks hitherto healthy infants aged 4—6 months with relatively acute symptoms in the beginning. According to KRABBE's description (2) the infant becomes restless and screams, developing attacks of tonic convulsions which gradually change to universal hypertonia with paroxysmal exacerbations. The increased tonus is provoked by external stimuli such as sound, light and touch, the clinical picture presented being that of decerebrated rigidity. The patient's posture is typical, with head turned back, lordosis of the spine, arms flexed, fists clenched and legs adducted and crossing each other, feet in the talipes position. Attempts at passive correction provoke paroxysmal convulsions with an increase of the above posture. Now and then there may be eclamptic fits of a clonic or tonic type. The tendon reflexes are increased or there may be areflexia paradoxa. There may be vomiting and constipation, and the constantly increasing mental deterioration ends in deep oligophrenia. Atrophy of the optic nerve and nystagmus are apt to occur, but there is no pathological change to be found in the cerebro-spinal fluid. There may be severe fever even in the absence of infectious complications, and the clinical picture seems to become worse with every bout of fever. Death usually occurs in the course of 4—5 months, the muscular hypertonia being often replaced by flaccid paralyses in the terminal stage.

Pathology: The brain preserves its form after the cranium is opened and feels as hard as cartilage. A microscopic examination shows that the grey matter is uninjured as a whole, whereas the white matter of the hemispheres is destroyed, being replaced by neuroglia which is to some extent fibrillary and to some extent presents abnormal, protoplasma-rich glia cells. What is said to be typical of this disease is the retention everywhere between cortex and corona radiata of a layer of undamaged medullary sheaths of a thickness of a couple of mm. This is the Meynert U-layer or stratum arcuatum. The white matter is also destroyed in the rest of the central nervous system, but not so completely as in the hemispheres.

KRABBE regards destruction of the white matter and necrosis of the neurites in the pyramidal cells in the cortex as the primary condition, and the increase of glia as a secondary phenomenon. Later writers have made observations which in their opinion are indicative of primary disease in the glia (3). It is not yet decided, apparently, whether the demyelinisation or the gliosis is the primary lesion, and the aetiology

of the changes observed would also seem to be obscure. But it is assumed that a hereditary anomaly of the metabolism affects the lipoid metabolism of the body.

Case no. 1. A female breastfed infant, E. E., born on August 28, 1947, was admitted to the Epidemiological Department of the Bergen City Hospital on August 2, 1948. Nothing to record about the family history. The parents were not related to each other; the age of the father being 41 and that of the mother (a primipara) being 26 at the birth of this child. The mother had been well during her pregnancy, and her confinement at term had been terminated by forceps delivery. The child was quite fit as soon as she was born, showing quite normal development. This was so both physically and statically, and from the psychic point of view during the first months of life.

When 4—5 months old she began to show striking and progressive lack of initiative. Gradually she could no longer hold her head up, and she seemed to be very feeble. During the last few months before admission to hospital the parents noticed that at times she could become stiff for a few seconds, particularly when she was exposed to sounds and the like suddenly. Now and then her expression had suggested suffering. She had been found to be febrile during the last few days before admission, but several weeks earlier she had often seemed to be hot when touched.

On admission she was found to be rather small for her age (70 cm), but well nourished, rather podgy (9.2 kg). Circumference of the head 47 cm. Fontanelle tension normal. No signs of rickets. She balanced her head badly, could not sit up without support and seemed feeble. Temperature 38° C. No tendon reflexes could be elicited. Babinski –. An ordinary physical examination yielded nothing else of interest.

About a week after admission it was noted that she now and then gave a somewhat absent-minded impression and presented a certain general rigidity. A week later she was flabby but her general condition was otherwise little affected by the high fever (see later on). There was constant rigidity which varied somewhat in intensity. The posture which she had now assumed and which was typical during the rest of her stay in hospital was as follows: She lay on one side with head bent back, arms flexed and legs extended, their extension being extreme in every joint with this exception that dorsiflexion of the big toes became gradually more marked. Tendon reflexes could never be elicited. She was very sensitive to sounds, touch and the like, reacting to them by violent screams. Throughout her stay in hospital the reactions of her pupils to light, direct and indirect, were very weak. During the last fortnight she was certainly blind. An ophthalmoscopic examination two months before death showed nothing abnormal.

The patient remained in hospital till her death on October 14th 1948, when she was 13 1/2 months old. During the first 6 weeks in hospital there were intermittent attacks of high fever, usually with great variations during the 24 hours and reaching a maximum of 41.7° C. She was subfebrile during the next three weeks, and at the end there was a rise of the temperature with terminal hyperpyrexia.

Special examinations: On admission the haemoglobin was 80 %, with 4.72 million erythrocytes, index 0.85, leucocytes 11.300. A differential count showed 20 % segmented neutrophiles, 70 % lymphocytes, and 2 % mononuclear leucocytes.

On August 4th 1948, an examination of the cerebro-spinal fluid showed cells 5, and a positive Fehling's reaction. No protein reactions were carried out as the cerebro-spinal fluid had become mixed with blood. Further examinations of the cerebro-spinal fluid showed:

On August 9th 1948, Cells 2, Pandy's test +, Nonne's test +, Heller's test + in dil. 1/20.
On August 14th 1949, Cells 2, Pandy's test + + +, Nonne's test +, Heller's test + in dil. 1/60.
On August 31st 1948, Cells not counted, Pandy's test +, Nonne's test +, Heller's test + in dil. 1/10.

Wassermann, Vidal and blood cultures were negative during the first few days in hospital. No abnormality was found on a radiological examination of the cranium, thorax and abdomen.

During the first fortnight in hospital penicillin and sulphonamides were given for the pyrexia without any effect. Acute pyuria was cured by four days' treatment with streptomycin. All other treatment was symptomatic only.

A post-mortem examination showed that the brain completely retained its shape on opening the cranium. On palpation the brain was quite as hard as cartilage (for the microscopic examination, see later).

Case no. 2. A male infant, Ø. E., born on October 12,1949, is the brother of case no. 1. Family history as given for this case. Detailed information was now obtained concerning the family histories of both parents in three generations. It was now stated that a paternal aunt had been insane in adult life.

The mother had been well during her pregnancy. Confinement at term and spontaneous. Weight at birth 4.250 g. During the first few months the parents stated that growth had been normal, the infant being active, smiling and snatching at objects at the usual time. When 6 months old and onwards, his static functions were seen to be slow, and when he was 11 months old, the writer was consulted because the parents feared he suffered from the same disease which had overtaken their first child. His general condition was now found to be good, his appearance was healthy, he took notice quite well, but was rather inactive. His back seemed to be weak, and he could not sit up or raise his body when he lay prone. His limbs seemed to move sluggishly, and it was very remarkable that he always held his legs extended. No definite changes of tonus, particularly no rigidity, was found. The tendon reflexes could not be elicited. He became gradually more and more languid and inactive, and from time to time he probably had bouts of fever as his parents found he was very warm when they touched him.

He was barely a year old when admitted to the Children's Clinic in Bergen on October 2, 1950. His state of nutrition on admission was good, and his colour normal. Temperature 38°C. He made a very languid impression, remaining quite immobile wherever he was placed. The tone of his limbs seemed to be normal. Tendon reflexes could not be elicited. He cried on movement, and from time to time he lay with extended limbs. The temperature rose still further after admission, and there was progressive exhaustion. It was now very noticeable that he began to whimper when undressed and attended to, and that he at once adopted a typical posture on these occasions, with head bent back and limbs extended. There was inward rotation of his arms, with thumbs adducted and flexed, and his legs showing extreme extension at every joint with the exception of his big toes which showed dorsiflexion. During these "spasm attacks" his legs also showed a tendency to cross each other, — a movement which became more plain when an attempt was made to lift them. His general condition became rapidly worse, and he died with high fever five days after admission to hospital.

Special examinations: Nothing abnormal found on an ordinary examination of the urine and blood. Syphilitic seroreaction (Meinicke) neg. Cerebro-spinal fluid: clear, cells 0, protein reactions negative. Pressure not measured. An ophthalmoscopic examination by an oculist showed normal optic discs and no pathological changes in the rest of the fundus.

A post-mortem examination was carried out at *Dr. F. G. Gade's Pathological-Anatomical Laboratory* in Bergen (Chief of the Pathological-Anatomical Department: Professor Erik Waaler M. D.):

From the description of the macroscopic examination, only the following will be quoted:

There is to some extent considerable diffuse injection of the lepto-meninges. The brain substance as a whole is of a curiously firm consistency with the result that the brain retains its shape on the table (the cerebrum and cerebellum as well as the brain stem). Under both frontal lobes in the anterior poles, the brain tissue is rather soft with the result that its substance is easily damaged while being detached."

The microscopic examination and description of the two cases:

Case no. 1. The grey matter is well preserved. The white matter is permeated by considerable quantities of proliferating glia of both the protoplasmatic and fibrillary type.

The first preparations examined gave the impression that the process was somewhat limited, and it was therefore taken to be an undifferentiated tumour. But on further scrutiny the changes found were indicative of a more diffuse prosess than was originally thought to be the case.

Case no. 2. Serial sections of the cerebrum and cerebellum were examined and all showed considerable gliosis with proliferation of large, non-differentiated glia cells. Thus the picture presented was exceedingly varied. Perivascular cell infiltration of plasma cells and lymphocytes was also seen, and at one point there was softening with marked infiltration of fatty granular cells (scanvenger cells). There was also considerable loss or disappearance of medullary sheaths.

Thus in brief it may be said that the microscopic picture presented a diffuse destruction of the white matter with glia proliferation and disappearance of medullary sheaths. In both cases this picture conforms to that which is seen in cases of acute infantile sclerosis of the brain of the Krabbe type.

Summary

The heredo-familial, degenerative diseases of the central nervous system are briefly reviewed, and an account is given of two cases of acute, diffuse, infantile sclerosis of the brain in a brother and sister. In both cases a typical picture developed from the fifth-sixth month of life, and death occurred after the disease had lasted about ten months. The family history yielded no data concerning diseases of the nervous system or the like, and the disease is taken to be the outcome of a recessive hereditary process.

Sclérose infantile diffuse aigüe du cerveau (Maladie de Krabbe). Observation de deux cas chez des frère et sœur.

Les maladies dégénératives héréditaires du système nerveux central sont brièvement passées en revue, et on expose deux cas de sclérose infantile diffuse aigüe du cer-

veau chez un frère et une sœur. Dans les deux cas, un tableau typique se développe à partir du 5-6ième mois de la vie, et la mort survient après une évolution de 10 mois environ. Dans l'histoire familiale on ne retrouve pas de données concernant les maladies du système nerveux central ou autre chose semblable, et la maladie est supposée lier à un processus héréditaire récessif.

Akute infantile diffuse Sklerose des Gehirnes (KRABBE'*sche Krankheit*). *Bericht über 2 Fälle bei Geschwistern.*

Die heredodegenerativen, familiären Krankheiten des Zentralnervensystems werden ausführlich geschildert und ein Bericht über 2 Fälle von akuter, infantiler diffuser Sklerose des Gehirnes bei Bruder und Schwester gegeben. In beiden Fällen hat sich das typische Bild im 5. und 6. Lebensmonat ausgebildet, der Tod war nach einer Krankheitsdauer von 10 Monaten eingetreten. Die Familiengeschichte enthielt keine Anhaltspunkte für derartige oder ähnliche Erkrankungen des Zentralnervensystems; die Erkrankung wird als Resultat eines erblichen, rezessiven Prozesses aufgefasst.

Esclerosis cerebral aguda difusa (*Enfermedad de Krabbe*). *Presentación de dos casos en hermanos.*

Se revisa brevemente esta enfermedad degenerativa, heredo-familiar del sistema nervioso central, y se hace la presentación de dos casos de forma aguda difusa de esclerosis cerebral en hermano y hermana. En ambos el cuadro clínico típico se desarrolló entre el quinto-sexto mes de la vida, falleciendo cuando la enfermedad llevaba ya diez meses de duración. En la historia familiar no había datos que hiciesen referencia al sistema nervioso y la enfermedad se considera como un proceso recesivo hereditario.

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The Waterhouse-Friderichsen Syndrome

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Introduction

The Waterhouse-Friderichsen syndrome (W.-F.) has been previously invariably fatal. Since the introduction of sulfa treatment about 20 cases of W.-F. or fulminating purpuric meningococcal septicaemia with recovery have been reported. These cases have had the same clinical picture as the cases of W.-F. with fatal outcome. As the cases of W.-F. at autopsy nearly always showed hemorrhages in the adrenals the question arose as to whether these hemorrhages were necessary for the clinical picture. — In view of recent discoveries of the relation between the pituitary and the adrenals it is possible to regard the problem from a new aspect.

As it is impossible to decide whether hemorrhages have been present in cases with recovery, where the clinical picture was identical with those which lead to death and where the autopsy revealed hemorrhages in the adrenals (W.-F.); these have all been called W.-F. in this article.

Up to the present date approximately 200 cases of W.-F. have been reported. The oldest patient was 65 years old (WEINBERG *et al.*) but 70 per cent of the cases reported were children under 2 years of age and 90 per cent under 9 years (RUCKS *et al.*). This hyperacute infectious disease is usually fatal within 36 to 48 hours.

Aetiology

In most cases the causative organism is the meningococcus. In a few cases, however, the staphylococcus, streptococcus, pneumoncoccus, and Coryne bacterium diphtheriae have been cultured (CAREY, PRATT-THOMAS *et al.*).

Symptomatology

The symptoms, only briefly outlined here, are the following. — The disease is hyperacute. Arises suddenly and is frequently preceded by a cold, a day or week before. The patient often has chills, complains of headache, and

vomits. The fever is nearly always very high. The most characteristic symptoms are intermittent or varying cyanosis (FRIDERICHSEN, MAGNUSSON *i.a.*) and postmortemlike lividity, purpura, collapse of the circulatory system, and low blood pressure which is usually not measurable.

At the examination the patient looks very ill. Often he is comatose. The hands and feet are often cold in spite of an elevated rectal temperature, i.e. there is a collapse of the circulatory system. Quite often no blood is obtained when sampling is attempted from fingerpricks.

EBERT *et al.* studied circulatory failure in acute infections. They found no evidence of significant haemoconcentration or of diminished blood volume. Nor did they find any increase in the venous pressure, which they believed to be due to a simultaneous cardiac lesion and lowering of the venous tension. According to these authors, this would mean that the entire cardiovascular system is affected by the infection.

The typical purpura may cover the entire body and often the rash may be seen on the conjunctivae and on the mucous membranes in the mouth. — MCLEAN *et al.* in 16 cases of meningococcal-bacteremia with purpura found meningococci on direct examination of smears from petechiae in 13 cases,but only in 10 cases with blood cultures, and in 12 cases with spinal fluid cultures.

Ordinarily, Kernig's and Brudzinski's signs are negative. The spinal fluid is usually normal or shows a somewhat increased cell content. The presence of several thousand cells in the spinal fluid, however, does not preclude the possibility of W.-F. The meningeal inflammation has been considered as indicating a greater resistance by the body, i.e. changes in the spinal fluid occur in those patients who have survived long enough to develop a metastatic meningitis (FROEHNER).

Low blood sugar values are often seen (MAGNUSSON i.a.) but normal or even high values occur.

The blood picture characteristic of W.-F. is a large number of W.B.C. and a shift to the left. The number of thrombocytes is usually normal or slightly reduced. As a rule, bleeding time, coagulation time, and prothrombin time are also normal.

Usually the urine does not contain albumin, casts, or red blood corpuscles. In the majority of cases there are elevated N.P.N. values.

If the function of the adrenals is reduced in W.-F. electrolytic changes might be expected to occur in the blood. Only in very few instances have one or several determinations of the electrolytes been reported. The values obtained are, furthermore, inconsistent.

CAREY and WEINBERG *et al.* have pointed out that electrolytic changes can not be expected in a disease which is so quickly fatal. Surviving patients have received immediately DOCA, adrenal cortical extract, blood transfusions, injections of sodium

chloride and glucose, etc., which naturally must affect the values of the blood electrolytes. It is known, moreover, that normal blood electrolyte values may also occur on isolated occasions in patients suffering from Addison's disease. — LOEB *et al.* demonstrated in dogs that even following total adrenalectomy the daily rate of excretion of sodium was as little as 2.3 milliequivalents per liter.

Pathogenesis

As mentioned before the autopsies of cases of W.-F. show very often hemorrhages in the adrenals. These hemorrhages are in 90 per cent bilateral. Cases have been described, however, where adrenal hemorrhages were insignificant or non-existent. Clinically, these cases could not be distinguished from W.-F. with hemorrhages in the adrenals. — WILLIAMS studied 17 cases of fulminating meningococcal septicaemia with purpura, collapse, and shock. He found adrenal hemorrhages in 9 cases but none in 8 cases. KINSMAN *et al.*, PRATT-THOMAS *et al.*, TURNER *et al.*, BANKS *et al.* and several others reported cases where adrenal hemorrhages could not be demonstrated; there were, however, other changes in the adrenal cortex which they described as "tubular degeneration," since the microscopic picture resembled that of the renal tubuli. These changes are believed to have arisen through necrosis and oedema in the fascicular and glomerular zones. GORDON *et al.* described one case of meningococcal septicaemia with necrosis of the pituitary gland. Only irregularly vacuolized cortical cells were observed in the adrenals. BANKS reported one case with focal necrosis and inflammation of the adrenal cortex, so-called "focal adrenalitis."

SARASON quoted, agreed with previous investigators who contended that the cortical cells increase mitotically in the zona glomerulosa, have their active phase in the zona fasciculata, and are destroyed in the zona reticularis. He noticed that the lipoids in the cortical cells disappeared in inflammatory diseases and cachexia.

RICH studied the adrenals in fatal acute infections with collapse of the circulatory system and found the above-mentioned "tubular" changes in the cortex. He is of the opinion that in these conditions necrosis and lysis occur primarily in the cells of the zona fasciculata. If the necrosis takes place in the central part, the marginal cells remain intact and the tubuli can be observed. In some cases, only isolated cells are necrotic and in others there are a few or many tubuli. RICH found these changes in infections with meningococci, streptococci, pneumococci, and Corynebacterium diphtheriae. He also examined the adrenals of patients with traumatic or surgical shock but did not find the aforementioned changes, which indicates that the shock itself is not the causative agent.

SELYE advanced similar views adding that there may be a close relation between so-called focal necrosis in the adrenal cortex, W.-F., and the disease of adaptation. Since it has been demonstrated in animal experiments that the exposure to particularly serious forms of stress can produce necrotic injuries in the adrenal glands, he found it likely that similar changes in man may be due to an excessive stimulation of the adrenal cortex.

FALOON *et al.* suggested a determination of the total number of eosinophil cells as an aid in the diagnosis of an impaired adrenal cortical function in W.-F. and also in the decision as to how long the therapy with cortical extract should be continued.

In the discussion of this disease many attempts have been made to explain why the hemorrhages have been confined to the skin and the adrenals. As has been shown previously the purpura can be explained as metastases of bacteria. The hemorrhages in the adrenals have been explained, in newborn and young children as being due to the greater bleeding tendency, the abundant blood vessel system in the adrenals, and hypostasis, all combined with septicaemia.

Nowadays the problem can be narrowed down: the adrenals are the target organ for hormones from the pituitary. During acute stress the pituitary forces the adrenals to a high or even maximal function through adrenocorticotropic hormone (ACTH). This maximal function can be maintained for only a short time. If the disease runs without successful treatment the adrenals collapse; the adrenals show the signs of exhaustion mentioned before or secondary hemorrhages may intervene.

Naturally it is very difficult to show definitely the high endogenous ACTH-production in this hyperacute disease. The clinical data from reported cases can not be compared because they must have been influenced by the rapidity with which the adrenals reach exhaustion; this time is not necessarily the same in all cases. These clinical data must have been influenced also by the therapy. — High values for 17-ketosteroids and 11-oxysteroids in the urine can be expected as during ACTH-therapy, but the patients receive nowadays adrenal cortical extract as imperative treatment and the values may be masked by this therapy. Such determinations have not been done hitherto as far as the author can see. — Nowadays it is probably possible to determine whether the serum content of ACTH is higher than normal (JONSSON *et al.*). This examination has not yet been done in this disease. — On the other hand there are indirect signs of augmented adrenal function, for example a large number of W.B.C. and a shift to the left and lymphopenia. In a few cases there have been low values of the serum albumin, which in connection with lymphopenia are found in Cushing's syndrome where a hyperfunction of the adrenal cortex is known to be present. — In some cases of W.-F. the blood sugar values are high. If the increased blood sugar values are found early in the disease, this too can be due to forced adrenal cortex function as seen occasionally during treatment with ACTH. In most cases of W.-F. the blood sugar values are low. This can be explained by the exhaustion of the adrenal cortex.

WEINBERG *et al.* found in a case of fulminating meningococcal septicaemia cephalin flocculation test + + + +, low blood cholesterol content in serum and decrease in the ester fraction. The values returned to normal as the pa-

tient recovered. — CONN *et al.* found after the administration of ACTH to a normal man that already after 48 hours there was a decrease in total serum cholesterol and in the ester fraction too. These changes did not develop after the administration of ACTH to patients with Addison's disease. This they explained as a possible indication that serum cholesterol is a probable precursor of adrenal cortical hormones. — If these two findings can be reproduced they, too, may speak for high ACTH-production and elevated function of the adrenal cortex during W.-F.

The significance of the constitution in W.-F. has been treated by some authors. MARTLAND reported 19 instances of W.-F. with massive bilateral hemorrhages in the adrenal cortex. In 3 of these cases an enlarged thymus was demonstrated, while the lymphoid tissue of the spleen and the intestinal region was not excessive. MAGNUSSON, too, reported one case with an enlarged thymus. CANUBI stressed the constitutional factor and suggested the name "meningococcic syndrome of the thymicolymphatic system." TRAINA, HOLMES *et al.*, and TURNER *et al.* were of a similar opinion. — Since in the fatal cases the disease has usually been of short duration and the thymus and the lymphatic glands have always shown a normal histologic picture, the enlarged thymus and the hyperplasia of the lymphatic tissue have been considered to have existed before the onset of the illness.

Therapy

The prognosis for a patient with fulminating purpuric meningococcal septicaemia or W.-F. depends primarily on early diagnosis and the institution of vigorous therapy against the infection as soon as the disease is suspected. HILL *et al.* suggested 1 000 000 I.U. of penicillin intravenously followed by 1 000 000 I.U. intramuscularly every second hour, to children 2 years of age. Most patients who have recovered, have received both penicillin and some sulfa preparation, usually Sulfadiazine. As substitutional therapy some adrenal cortical extract should be given; the initial dose should preferably be administered intravenously. By repeated daily counts of the total number of eosinophil cells the dosage of cortical hormone can be controlled as mentioned before. — Most cases with recovery received DOCA. Noradrenalin should be given against shock rather than adrenalin. Since the patient often vomits he requires fluids parenterally. Plasma or whole blood does not seem to offer any advantages over salt-glucose. Large doses of ascorbic acid should be given since the rapid liberation of cortical hormone must be assumed to exhaust swiftly the ascorbic acid supply of the adrenal cortex. By means of continuous determinations of blood pressure and serum electrolytes and by repeated ECG the danger of overdosage with DOCA, cortical extract or salt-glucose solutions could be avoided.

Conclusion

On the basis of the above-mentioned data from other investigators and the writer's own experience it is stressed that the Waterhouse-Friderichsen syndrome or fulminating purpuric meningococcal septicaemia is a hyperacute infectious disease which is rapidly fatal if the infection is not quickly controlled. On account of the extensive infection and large production of toxin, the entire vascular system is damaged with ensuing circulatory collapse. The functions of the adrenal cortex are accelerated by the violent stress of the infection, causing a more rapid liberation of steroids. When the infection is not controlled, the adrenal cortex cannot maintain this hyperfunction, the cells necrose and undergo lysis and oedema develops. These changes are at first reversible. By means of intensive therapy the stress on the adrenal cortex can be reduced and the cortical function can be somewhat relieved by the administration of cortical extract. The tubule formations in the cortex constitute a locus minoris resistentiae. The hemorrhages in the cortex are a secondary phenomenon and probably of no significance for the clinical picture or the outcome of the disease.

Most cases of so-called Waterhouse-Friderichsen syndrome or fulminating purpuric meningococcal septicaemia succumb and the autopsy shows very often hemorrhages in the adrenal cortex. Only these cases should be called Waterhouse-Friderichsen syndrome as the original cases with this name showed hemorrhages in the adrenals. Most often the causative organism in W.-F. in this sense and also in cases with recovery is the meningococcus. Therefore, the cases reported have often been denominated by fulminating purpuric meningococcal septicaemia. As some cases with the same clinical picture have been reported with other causative organisms it would perhaps be better to call them all fulminating purpuric septicaemias.

Summary

Fulminating purpuric meningococcal septicaemia with recovery cannot be separated clinically from the Waterhouse-Friderichsen syndrome. The name Waterhouse-Friderichsen Syndrome should be reserved for those cases in which the autopsy shows hemorrhages in the adrenal cortex. As the causative organism is not always the meningococcus the name fulminating purpuric septicaemia is suggested instead of fulminating purpuric meningococcal septicaemia. The author discusses the works of other investigators who assert that hemorrhages in the adrenal cortex are not always present in cases of fulminating purpuric meningococcal septicaemia, and that, where they occur, they are not likely to be of any consequence for the clinical picture or the outcome of the disease. The relation between the pituitary and the adrenals is discussed and data are compiled, pointing to the possible high endogenous ACTH production leading to high or maximal function of the adrenal cortex. It is the author's opinion that the fatal outcome in fulminating purpuric septicaemia is caused by the hyperacute infection, the shock, and the exhaustion of the adrenal cortex. If patients suf-

fering from this disease are to have any chance of recovery, an early diagnosis, vigorous therapy against the infection, and substitutional therapy with adrenal cortical extract are essential.

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BOOK REVIEWS

R. Martin du Pan: **Contribution a l'étude des relations entre l'âge et l'immunité pendant la jeunesse.**

S. Karger A.-G., Basel, 1952. Sfr. 8.

The author begins with a short historical survey of the natural and acquired immunity in infancy and childhood. His own experiments are firstly concerned with the electrophoretic pattern of the mother's serum and the new-borns. The content of γ-globulin is usually elevated in the placenta and in the new-borns. The author has used blood obtained from the placenta as treatment for different conditions with good results. Further he has studied an outbreak of an infectious disease in a nursery home for infants and in the adjoining hospital, as well as the frequency of ordinary upper respiratory infections in several schools. He concludes that the resistance to these infectious diseases is augmented with age.

The author has vaccinated a number of infants of different ages with polysaccharides of pneumococci and with triple-vaccine (vaccine against tetanus, diphtheria and whooping-cough) confirming the American results showing that it is as a rule possible to obtain good serological response by vaccination started at the age of 2—3 months.

The author's materials are limited and are not statistically treated but give informations in a very interesting field.

R. Lagercrantz, Stockholm.

Fritz Hauser: **Störungen der Fettresorption im frühen Säuglingsalter.**

Bibliotheca Pædiatrica. Suppl. ad Annales Pædiatrici no. 53, 1952. S. Karger, Basel. Sfr. 14: —.

After a discussion on the theories of fat absorption, where the author accepts the phosphorylation theory of Verzàr, a detailed description is given on different methods of investigating the fat absorption in infants (vitamin A absorption tests, chylomicron counting, fat balances etc.). The author uses balance periods of only three days' duration. The fecal fat is determined in dried feces acc. to Tidwell & Holt: J. Biol. Chem. *112:* 605, 1936.

A lengthy description is given on the clinical course of patients with impaired fat absorption.

The author has determined the fecal losses of fat in premature infants, in newborn full term infants, and in infants with erythroblastosis with liver damage. He found that the fat absorption is somewhat lower than normal during the first two weeks of life in full term infants and for a little longer period in premature infants. In patients with erythroblastosis impairment of fat absorption is parallel to the degree of icterus. Whereas normal fat absorption is found to be around 95 per cent of the fat ingested (human milk), the author found an absorption of 85–90 per cent in most premature

and newborn infants. In rare instances the fat absorption was below 80 per cent. In a few experiments with fat-enriched human milk the premature infants showed a good increase in weight and most of the additional fat was absorbed.

Although the monograph is stated to be printed in 1952, the most recent references are from 1950. Several of the diagrams and tables mentioned in the text are not included in the book.

Lars Söderhjelm.

Correction

The table p. 551 in the article of Svend Heinild, Present-Day Tasks in Psychosocial Paediatrics, Acta Pædiat. 41: 539, 1952, has been wrongly printed. The correct table is reprinted below.

The following are examples of the use of this diagnostic system:

Case I	Case II
Vit. domest.	*Streptococcosis.*
(Parents divorced).	Chronic rhinopharyngitis.
(Rearing by grandparents).	Sinusitis.
(Authoritative education).	Ad. veg.
Insomnia.	
Nail biting.	*Vit. domest.*
Sensitive constitution.	(Disharmonious marriage).
Leptosomia.	Refractoriness.
	Aggression.
Streptococcosis.	Eating problem.
Adenitis colli.	Anxiety neurosis.
Albuminuria.	Intellectual superiority.